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**Incident Diabetes Associated with Second-Generation Antipsychotic Therapy:
An Evaluation of the Impact of Dose and Treatment Indication**

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**Incident Diabetes Associated with Second-Generation Antipsychotic Therapy:
An Evaluation of the Impact of Dose and Treatment Indication**

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The impact of antipsychotic dose and treatment indication on the risk of new-onset diabetes associated with use of second-generation antipsychotic (SGA) monotherapy were assessed using medical data from Texas Medicaid. Eligible enrollees aged ≥ 18 years of age were followed for a maximum of 12 months between 1997 and 2001. Patients were stratified according to treatment dose (low, medium, high) and a hierarchy of mutually exclusive diagnostic categories: schizophrenia; bipolar disorder; dementia; psychotic disorder; non-psychotic disorder; and no mental health indication.

The average patient age (N=19,430) was 60.3 years (SD: 21.9); the majority of whom were White (55.1%) females (65.7%) aged ≥ 60 years (50.4%). At treatment-onset, the prevalence of diabetes was 16.9%. The mean (SD) dose for the most prevalent conditions (schizophrenia, bipolar disorder and dementia,

respectively) were as follows: olanzapine (12.04mg (6.73); 8.91mg (5.78); 4.87mg (3.00)); quetiapine (273.16mg (203.86)); 146.33mg (142.29); 79.59 (82.57)); and risperidone (3.55mg (2.37); 2.05 (1.76); 1.12 (0.85)). The incidence of diabetes was 2.37%. After controlling for demographic, clinical and medication variables, no difference ($p=0.281$) was noted in the incidence of diabetes according to the specific SGA used ($N=7,842$). Compared to risperidone, the odds of new-onset diabetes were 0.879 (95% CI: 0.653 to 1.184) and 0.683 (95% CI: 0.414 to 1.126) for olanzapine and quetiapine, respectively. Neither treatment indication ($p=0.876$) nor dose ($p=0.274$) were associated with the development of diabetes. When examined according to the individual SGA, the incidence of diabetes did not differ ($p\geq 0.292$) according to antipsychotic dose or treatment indication for quetiapine and risperidone. For olanzapine, while no difference was noted according to the dose used ($p=0.384$), the incidence of diabetes differed according to the treatment indication ($p=0.034$), with a significant increase in the odds of diabetes noted for those with a psychotic disorder (OR: 2.911, 95%CI: 1.088 to 7.790) or a non-psychotic disorder (OR: 2.433, 95%CI: 1.042 to 5.680) compared to schizophrenia.

Results indicate that the risk of new-onset diabetes does not differ among the SGA agents. While the dose of antipsychotic prescribed varied significantly according to treatment indication and patient age, neither dose nor treatment indication were associated with the development of diabetes.

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Chapter 1: Introduction and Literature Review

1.1 Problem Statement

Diabetes mellitus is a chronic disabling disease that is associated with significant morbidity and mortality.¹ The estimated prevalence of diabetes in the United States (U.S.) was 6.2 percent in 2000 (17 million people) of whom 35 percent (5.9 million) were undiagnosed.² Studies have suggested an increased risk of diabetes of two- to three-fold in patients treated with second-generation antipsychotic agents.^{3;4} This has significant ramifications in terms of both the economic cost of treatment and the disease burden for patients treated with these agents. Based on information from case studies reported in the literature, there appears to be an alarming risk of diabetic ketoacidosis in patients treated with second-generation antipsychotic agents.⁵⁻⁸ This is a medical emergency; the evaluation and treatment of which may be complicated if the patient has concurrent psychosis.

While glucose dysregulation appears to be associated with the use of second-generation antipsychotic agents, it is difficult to ascertain the extent of the problem. Glucose dysregulation appears to be independent of second-generation antipsychotic dose although the evidence is conflicting.^{3;9;10} The dose of antipsychotic prescribed depends on the indication for which it is prescribed.^{11;12} For example, the dose used to treat schizophrenia differs from that used to treat dementia-related behavioral problems.^{11;12} Differences in dose may explain differences in the relative risk of developing diabetes. Alternatively, these differences may reflect the differing propensities of patients to develop diabetes mellitus as documented by reports of a higher prevalence of diabetes mellitus in patients with schizophrenia and bipolar disorder than in the general population that is independent of antipsychotic treatment.¹³⁻¹⁸ Patient age is an

important confounding variable. Regardless of treatment indication, older patients typically are prescribed lower doses due to decreased metabolism and poorer tolerance of these agents.^{11;12} In addition, patients with serious mental illness, including schizophrenia and bipolar disorder, are at significantly higher risk for premature death than the overall population.¹⁹ Previous studies with a preponderance of older patients may have included disproportionate numbers with dementia and other psychotic disorders, conditions for which risperidone is more frequently prescribed in clinical practice than olanzapine. The combination of lower treatment doses in this population, and the fact that older patients may lack the diathesis for developing diabetes, may have skewed study findings. As a result, studies that do not control for treatment indication and dose may favor one second-generation agent over another in terms of the risk of new-onset diabetes.

In September 2003, the Center for Drug Evaluation and Research (CDER) requested that the labeling for second-generation antipsychotic agents be changed to acknowledge the perceived association between the use of these agents and the development of hyperglycemia.²⁰ In requesting this change, the CDER acknowledged the limitations of the available data, particularly in relation to the potential impact of confounding variables and the ability to determine the relative risk of the different second-generation antipsychotic agents. They highlighted the need for additional research to assess this relative risk and to identify patient sub-groups that may be more susceptible to this adverse event. To this end, the purpose of this study is to examine the impact of antipsychotic dose and treatment indication, on the association between second-generation antipsychotic use and development of diabetes mellitus.

By answering these questions, the risks and benefits associated with the use of the various agents can be assessed with greater clarity. Research in this

area will also impact the future management of psychotic patients in terms of screening and surveillance for diabetes mellitus.

1.2 Literature Review

To provide context to this study, a general overview of current treatment practices regarding the therapeutic use of second-generation antipsychotic agents is provided. Specifically, the use of these agents in schizophrenia, bipolar disorder, other psychotic disorders, dementia and in other non-psychotic mental disorders is examined. A comprehensive review of the metabolic disturbances associated with the second-generation antipsychotic agents, including a critical review of the studies published in this area is then presented. An overview of diabetes mellitus (hereafter referred to as diabetes), with particular emphasis on diabetes in patients with mental health disorders is included as additional background material. As the focus of this study relates to the potential impact of dose and treatment indication on the occurrence of antipsychotic-induced new-onset diabetes, a comprehensive section on the prescribing patterns of these agents is included. The proposed study will use a secondary database; therefore, the use of such large claims databases in health outcomes research is discussed, with particular emphasis on the Medicaid claims database. This chapter concludes with the rationale and objectives for the study together with a detailed list of hypotheses.

1.3 Section 1 - General Background on Schizophrenia

The purpose of this section is to provide a brief overview of schizophrenia – its characteristics, classification and management.

1.3.1 Epidemiology

Schizophrenia affects between 0.5 and one percent of the adult population.²¹ Although the prevalence is similar for men and women, the age of onset differs.²² The median age of onset is the early to mid twenties for men and the late twenties for women. Schizophrenia rarely presents before adolescence or after the age of 40 years.²²

1.3.2 Etiology and Pathogenesis

The etiology of schizophrenia is unknown. There is evidence of a genetic basis to the disease with an increased prevalence of ten percent noted if a first-degree relative is affected, and three percent if a second-degree relative is affected when compared to the general population.²³ A greater concordance has been documented in monozygotic twins than dizygotic twins.²³ Similarly, adoption studies indicate an increased risk of illness among adopted children whose biological mothers have schizophrenia.²³ Environmental factors such as prenatal, perinatal and childhood brain injury have also been associated with an increased risk of schizophrenia.²³

There are no laboratory findings that are diagnostic of schizophrenia; however, research has centered on the hypothesis of increased dopamine activity. Evidence for dopamine overactivity includes: the strong correlation between the extent of dopamine D₂ receptor blockade and antipsychotic drug efficacy; the exacerbation of the signs and symptoms of schizophrenia by dopamine agonists; and the reports of increased dopamine D₂ receptors density seen by positron-emission tomography, and at autopsy, of patients with schizophrenia.²⁴

Serotonergic and glutamergic dysfunction have also been hypothesized to be etiologic in schizophrenia.²⁴ A variety of anatomic abnormalities have been associated with schizophrenia, including enlargement of the lateral and third ventricles and reduction in the size of the limbic and prefrontal cortex brain areas.²⁵ However, no single neuroanatomic defect has been consistently demonstrated in patients with schizophrenia.²⁵

1.3.3 Classification and Clinical Characteristics

Schizophrenia is a psychotic disorder. The characteristic symptoms of schizophrenia are grouped into three categories: positive symptoms; negative symptoms; and cognitive deficits. Positive symptoms typically relate to a distortion or excess of normal function and include delusions and hallucinations.²² Negative symptoms relate to a diminution of normal process and include affective flattening, alogia, anhedonia and avolition.²² Cognitive deficits include alterations of attention, working memory, and executive function. To confirm a diagnosis of schizophrenia, two or more of these symptoms must persist for at least one month, with some of the symptoms persisting for at least six months.²² Several subtypes of schizophrenia exist. These are defined according to the predominant symptoms at the time of evaluation and may, therefore, change over time. The subtypes include: paranoid; disorganized; catatonic; undifferentiated; and residual types.²² The disease is further specified according to the time course of the illness, with course specifiers including: episodic with and without interepisode residual symptoms; continuous; single episode in partial or full remission; and other or unspecified pattern.²²

1.3.4 Course

The onset of the schizophrenia may be abrupt or insidious.²⁶ The clinical course is variable with the majority of patients displaying exacerbations, in the

form of acute psychotic episodes, and remissions.²⁶ Following remission of an acute psychotic episode, residual features typically remain.²⁶ These vary in severity but can include: anxiety; suspiciousness; and lack of volition, motivation, insight and judgment. As a consequence, the majority of patients with schizophrenia experience impairment of occupational and/or social function.²¹ Complete remission is rare and the long-term prognosis for most patients is poor.^{21;27} Epidemiological studies have demonstrated a steep decline in survival over the initial two to five years following diagnosis, plateauing thereafter.²⁷ Schizophrenia is associated with an increased incidence of comorbidities including substance misuse, other mental disorders and general medical conditions.²⁷ These, combined with a lifetime prevalence of suicide of approximately ten percent, contribute to an increased mortality rate in patients with schizophrenia.²²

The American Psychiatric Association describes three phases of schizophrenia: an acute psychotic phase; a stabilization phase in which the acute psychotic symptoms decrease in severity; and a stable phase in which symptoms are stable and typically less severe than in the acute phase.²¹ As stated, most patients alternate between these phases achieving full or partial remission during the stable phase. With treatment, approximately 30 percent of patients achieve partial but good responses, a further 30 percent achieve partial but inadequate responses and the remainder experience chronic deterioration. Approximately 10 percent of patients experience continuous psychotic symptoms.²⁸ A number of factors are predictive of a better prognosis including: being female; married; having an abrupt onset of illness with a good premorbid function; and minimal comorbidity.²⁶ However, these account for only a small percentage of outcome variance. As schizophrenia is a disease characterized by multiple relapses, long-term treatment is recommended.²⁸ In the absence of continuing prophylaxis, up to

75 percent of patients will relapse with an acute psychotic episode within six to 24 months.²⁸

1.3.5 Treatment

Drug therapy, in particular with antipsychotics, forms the mainstay of schizophrenia management. The management of schizophrenia was revolutionized with the discovery of chlorpromazine in the 1950s.²⁹ Multiple antipsychotic agents have since been developed. These agents are broadly divided into two classes: ‘typical,’ ‘conventional,’ or ‘first-generation’ agents and ‘atypical,’ ‘new,’ or ‘second-generation’ agents, the prototype of which is clozapine. The latter is generally accepted to refer to an antipsychotic agent with a low propensity to cause extrapyramidal side-effects or a sustained increase in prolactin levels.³⁰ Hereafter, the terms ‘first-generation’ and ‘second-generation’ will be used to distinguish the classes. Non-drug treatments, such as psychosocial rehabilitation programs, are used as adjunctive measures. This section provides information on the pharmacotherapy of schizophrenia, with particular emphasis on the second-generation or atypical antipsychotic agents. The section concludes with a brief overview of the role of non-drug therapy.

1.3.5.1 First-Generation Antipsychotics

First-generation antipsychotic agents include: chlorpromazine; fluphenazine; haloperidol; perphenazine; trifluoperazine; thiothixene; and thioridazine. These agents are further stratified into low and high-potency agents based on the minimum amount of drug in milligrams required to achieve the desired antipsychotic effect. High-potency agents include haloperidol and fluphenazine, and have a daily dose of a few milligrams, whereas low-potency agents include chlorpromazine and thioridazine which have higher daily doses.²⁹

1.3.5.1.1 Mechanism of Action

The exact mechanism of action of the antipsychotic agents has not fully been elucidated. These agents inhibit dopamine, specifically dopamine D₂ receptors.²⁴ Relief of positive psychotic symptoms occurs when 60 to 65 percent of D₂ receptors are occupied while increasing occupation of these receptors to 77 percent or more, is associated with extrapyramidal side effects.²⁴ The first-generation antipsychotic agents are characterized by having a high affinity of between 70 and 90 percent for dopamine D₂ receptors.²⁴ The relative affinities of the agents for these, and other receptors, including serotonin 5-HT_{2A} and 5-HT_{2C}, dopamine D₁ and D₄, α_1 -adrenergic, histaminic and cholinergic receptors, appears to differentiate the antipsychotics in terms of adverse effect profiles.²⁴

1.3.5.1.2 Efficacy

The efficacy of the first-generation antipsychotics in the acute management of schizophrenia is well established.²⁹ These agents have been demonstrated to reduce the intensity of positive symptoms, shorten acute episodes or exacerbations, and reduce the likelihood of recurrence.²⁹ These agents appear to have little effect on affect, cognitive symptoms or negative symptoms.³⁰ There is considerable heterogeneity of response to the first-generation agents, with between 10 and 20 percent having a minimal response to treatment and a smaller percentage being considered to be treatment refractory.²⁹ These agents are considered equally effective when used in equipotent doses; therefore, the clinical choice depends on the adverse effects profile.²⁹

1.3.5.1.3 Adverse Effects

Although as a class these agents all cause similar adverse effects, they differ in their propensity to do so. Adverse effects include: antihistaminic (sedation); antidopaminergic D₂ (extrapyramidal side-effects and

hyperprolactinemia); anticholinergic (dry mouth, blurred vision, constipation, urinary retention, sinus tachycardia, cognition and memory effects); and anti- α_1 -adrenergic effects (reflex tachycardia and orthostatic hypotension).³¹ Typically, the lower potency agents cause more sedation and hypotension, and the high potency agents more extrapyramidal side effects.³² These include: dystonia; akathisia; pseudoparkinsonism; and tardive dyskinesia which can occur at rates of up to 64, 36, 59, and 20 percent, respectively.³² It is the extrapyramidal effects, particularly tardive dyskinesia, that limit the usefulness of these agents relegating them to second-line therapy in clinical practice. Among the first-generation antipsychotics, the low-potency agents, in particular chlorpromazine have been associated with glucose intolerance.³³

1.3.5.2 Second-Generation Antipsychotics

The first agent in this class, clozapine, was licensed in the United States (U.S.) in 1989.³⁴ Agents currently available in the U.S. in 2006 are: aripiprazole; clozapine; olanzapine; quetiapine; risperidone; and ziprasidone. These agents, with the exception of clozapine, are now established as first-line therapy for the management of schizophrenia. (Table 1.1)

Table 1.1: Licensed Doses for the Second-Generation Antipsychotic Agents

Drug (Indication)	Initial Dose	Titration Rate	Target Daily Dose	Maximum Daily Dose (MDD)	Comments and Dose Adjustments in Specific Populations
Aripiprazole ³⁵ (SCZ)	10-15mg qd	Not before 2 weeks	10-15mg qd	30mg	No ↑ in efficacy noted with doses >15mg ↑ or ↓ dose when used with inducers or inhibitors of cytochrome P450
Aripiprazole ³⁵ (BIP)	30mg qd	N/R	15-30mg qd	30mg	Dose ↓ to 15mg in 15% of patients in flexible dose trials based on tolerability
Clozapine ³⁶ (Resistant SCZ)	12.5mg qd/bid	25-50mg/qd until at TDD, then ≤100mg qd 1-2 x week	300-450mg qd (at 2 weeks) MDD = 600mg	100-900mg qd No safety data for doses >900mg qd*	Maintenance phase: use lowest possible dose to maintain remission
Clozapine ³⁶ (Recurrent/ suicidal behavior in SCZ/SAD)	12.5mg qd/bid	N/R	MDD = 300mg (12.5 – 900mg)	As above	As above
Olanzapine ³⁷ (SCZ)	5-10mg qd	5mg/qd q week	10-20mg	No safety data for doses > 20mg qd*	No ↑ in efficacy noted with doses >10mg Debilitated patients / slow metabolism 5mg qd starting dose
Olanzapine ³⁷ (BIP)	10-15mg qd	5mg/qd q24 ⁰	5-20mg	No safety data for doses > 20mg qd*	As above
Quetiapine ³⁸ (SCZ)	25mg bid	25-50mg bid or tid q24 ⁰ -48 ⁰	300-400mg qd	150-750mg No safety data for doses > 800mg qd	No ↑ in efficacy noted with doses >300mg Elderly / hepatic impairment: ↓dose and titrate slower: start 25mg qd, ↑ 25-50 qd
Quetiapine ³⁸ (BIP)	50mg bid	50mg bid q24 ⁰	400-800mg qd	No safety data for doses > 800mg qd*	As above

Table 1.1: Licensed Doses for the Second-Generation Antipsychotic Agents (continued)

Drug (Indication)	Initial Dose	Titration Rate	Target Daily Dose	Maximum Daily Dose (MDD)	Comments and Dose Adjustments in Specific Populations
Risperidone ³⁹ (SCZ)	1mg bid	1mg bid/ qd	Acute phase: 3mg bid Maintenance phase: 4mg qd	4-8mg qd No safety data for doses > 16mg qd*	Elderly /debilitated /renal /hepatic impairment ↓ dose and titrate slower: 0.5mg bid, ↑ 0.5mg bid/qd and then q week when reach 1.5mg bid No ↑ in efficacy noted with doses >6-8mg
Risperidone ³⁹ (BIP)	1-1.5mg bid	1mg qd	1-6mg qd	6mg qd	Not indicated for long-term treatment (> 3 weeks)
Ziprasidone ⁴⁰ (SCZ)	20mg bid	20mg bid	20-80mg bid	>80mg bid usually not recommended No safety data for doses > 200mg qd*	None
Ziprasidone ⁴⁰ (BIP)	40mg bid	20-40mg bid on day two	40-80mg bid	As above	Mean daily dose in clinical trial = 120mg qd

Abbreviations: SCZ – Schizophrenia; SAD – Schizoaffective Disorder; BIP – Bipolar Disorder; Tx - Treatment; N/R – not reported; MDD – Maximum Daily Dose; TDD – Target Daily Dose; qd – once daily; q24⁰ – every 24 hours; q48⁰ – every 48 hours; bid - twice daily; tid - three times daily; q week – every week

* According to the product package insert.

1.3.5.2.1 Mechanism of Action

As noted previously, the exact mechanism of action of the antipsychotic agents has not fully been elucidated. The second-generation agents all inhibit dopamine D₂ receptors, but to a lesser extent than the first-generation agents. For example, clozapine occupies only 38 to 63 percent of D₂ receptors.²⁴ This is lower than the threshold of 77 percent occupancy associated with extrapyramidal side-effects thereby explaining the decreased propensity of these agents to cause this problem.²⁴ A notable exception is risperidone, which at daily doses greater than six milligrams typically exceeds the threshold occupancy rate for extrapyramidal side-effects.²⁴ The second-generation agents exhibit a high affinity for serotonin 5-HT_{2A} receptors although the clinical significance of this is not fully known.³⁰ Aripiprazole is unique among the second-generation antipsychotics, in that it acts as a partial agonist at dopamine D₂ and serotonin 5-HT₁ receptors.³¹ The second-generation agents have varying effects on multiple other neurotransmitters including: dopamine D₁ and D₄ receptors; histamine H₁; serotonin 5-HT_{2C}; cholinergic; and α 1-adrenergic receptors.³⁰ As a result, this group is heterogeneous both in terms of efficacy and tolerability.

1.3.5.2.2 Efficacy

The second-generation agents are more effective than placebo in treating both the positive and negative symptoms of schizophrenia, although the magnitude of the effect is deemed only to be moderate (mean effect size = 0.25 (95% confidence interval (CI): 0.22-0.28)).^{41;42} When compared to the first-generation antipsychotics, these agents have been found to have comparable efficacy in treating the positive symptoms, and superior efficacy in treating both the negative symptoms and cognitive deficits of schizophrenia, although heterogeneity of effect has been seen.⁴¹⁻⁴³ The superiority of the second-generation agents is disputed with assertions that the differences are based on

inappropriate comparator doses and that the available studies were short-term in nature.⁴⁴ In clinical practice, the second-generation agents have been deemed more effective than the first-generation agents due to a lower propensity to be prematurely discontinued.⁴⁵

Clozapine, which is reserved as a second-line agent due to its toxicity, has been demonstrated to be effective in treatment resistant schizophrenia, with 60 percent of patients responding within six weeks.⁴⁶ Clozapine is also indicated for reducing suicidal ideation in at-risk patients although a reduction in the rate of death by suicide is yet to be confirmed.^{36;47;48}

1.3.5.2.3 Adverse Effects

As with the first-generation agents, the second-generation antipsychotics can cause a wide range of adverse effects including: antihistaminic; antidopaminergic D₂; anticholinergic; and anti- α_1 -adrenergic effects.³¹ Comparatively, however, the second-generation agents are more tolerable. In particular, the second-generation agents, with the exception of risperidone, have a reduced propensity to cause extrapyramidal side effects. When used at doses greater than six milligrams a day, risperidone has a similar risk of extrapyramidal effects as haloperidol. Agranulocytosis, occurring at a rate of 0.39 percent, myocarditis and an increased propensity to lower the seizure threshold, are important side effects associated with clozapine and limit its use to that of second-line therapy.³⁶ The risk of metabolic side effects with the second-generation agents, including the potential for: weight gain; glucose dysregulation; dyslipidemia; hyperglycemia; pancreatitis; and hyperprolactinemia will be discussed in detail in section 6.

1.3.5.3 Other Drugs Used in the Treatment of Schizophrenia

Several classes of drugs are used in addition to the antipsychotic agents in the management of schizophrenia. These are primarily used as adjunctive therapy

to treat either comorbid conditions or to alleviate adverse effects of the antipsychotic agents. A brief description of their role in therapy follows.

1.3.5.3.1 Benzodiazepines

Benzodiazepines are primarily used as adjunctive therapy to antipsychotics in patients experiencing acute exacerbations, particularly with severe anxiety, agitation, or irritability.⁴⁹ They are used for their anxiolytic or sedative-hypnotic properties as opposed to having a direct impact on psychotic symptoms.⁴⁹ They have been used acutely in lieu of intramuscular antipsychotics, but in combination with maintenance antipsychotic therapy in the management of acute agitation and aggression.⁴⁹ Use of these agents is complicated by their side-effects including sedation, ataxia and dependence.⁴⁹

1.3.5.3.2 Mood Stabilizing Agents

The use of lithium and anticonvulsants is recommended as adjunctive therapy in the management of schizophrenia. These agents are used to improve labile affect and agitation.⁴⁹ Despite their widespread use there is limited empirical evidence to support this.^{50;51} The use of these agents is complicated by their adverse effects. These may be additive to those of the antipsychotic agents, or complicate their use, and include weight gain, liver toxicity and enzyme induction.^{31;50}

1.3.5.3.3 Antidepressants

Depression is a significant comorbidity in schizophrenia with an estimated prevalence of 25 percent.⁵² Antidepressants are indicated as adjunctive treatment for patients with comorbid depression, obsessive compulsive disorder or panic attacks.⁴⁹ The use of these agents may be complicated by overlapping toxicities between the antidepressants and the second-generation antipsychotics.^{31;49} There is also potential for clinically significant drug-drug

interactions due to the inhibitory effects of certain antidepressants on the cytochrome P450 enzyme system.³¹

1.3.5.3.4 Antiparkinson Agents

Agents such as benztropine, procyclidine and trihexyphenidyl are widely used in patients with schizophrenia to prevent or alleviate the extrapyramidal side-effects caused by the antipsychotic agents.⁴⁹

1.3.5.4 Treatment Algorithms

A number of treatment algorithms have been developed to aid clinicians in selecting a drug.^{21;53} One that is widely used is the Texas Medication Algorithm Project (TMAP). This advocates the use of the second-generation antipsychotic agents as first and also as second-line therapy. Following failure of two agents, use of either clozapine or another first or second-generation agent is recommended as third-line. Combination antipsychotic therapy should only be considered after exhaustion of all of these options.⁵³

1.3.5.5 Non-Drug Therapy

Non-pharmacological measures are ancillary to pharmacological management and have been documented to be beneficial in preventing relapse, improving social and vocational functioning, and increasing coping skills and independent function.²¹ Treatments include psychosocial interventions such as individual, family and group therapy.²⁸ Social and community interventions focus on coordinating care and providing social support such as in community case management programs.²⁸ Non-pharmacological measures also focus on patient rehabilitation and include social skills training and vocational rehabilitation.²⁸ While the quality of controlled clinical trials is variable, there is evidence that these programs are effective in reducing hospitalization rates and improving social functioning.^{21;28}

1.3.6 Summary

Second-generation antipsychotics are established treatment for the acute and long-term management of schizophrenia. Clozapine aside, there is little compelling evidence to discriminate between the agents based on efficacy. These agents differ in terms of their tolerability, although differences in the relative potential to induce diabetes are yet to be confirmed. Given the apparent association between schizophrenia and diabetes, it is imperative that the relative potential of these agents to induce diabetes be clarified so that their respective roles in therapy can be more clearly delineated.

1.4 Section 2: General Background on Bipolar Disorder

In this section an overview of bipolar disorder, including its epidemiology, course and management, is provided.

1.4.1 Epidemiology

Bipolar disorder is a common mental disorder that affects between 1.5 and 3 percent of the population.⁵⁴ Bipolar I disorder affects both men and women equally, with a median age of onset of 20 years and an estimated prevalence of 0.4 to 1.6 percent.⁵⁵ Bipolar II disorder occurs in approximately 0.5 percent of the population and is thought to be more common in women than men.^{22;55}

1.4.2 Etiology and Pathogenesis

The precise etiology of bipolar disorder is unknown.⁵⁵ There is considerable evidence for a genetic basis to the disease although the mode of transmission is unknown. First-degree relatives of patients with bipolar disorder have a 15 to 35 percent risk of developing a mood disorder.⁵⁶ Twin studies also support this hypothesis, with concordance rates of 78 to 80 percent documented in monozygotic twins, compared to 20 percent in dizygotic twins.⁵⁶

Dysregulation of the neurotransmitters, specifically a relative excess of norepinephrine and dopamine in mania, and a functional deficit of these neurotransmitters together with serotonin in depression, have been implicated in the pathogenesis of bipolar disorder.⁵⁶ Disturbances in thyroid activity, calcium and sodium homeostasis together with abnormalities in membrane transport and secondary messenger systems have also been implicated.⁵⁶ A biological rhythms hypothesis has also been proposed based on observed seasonal trends in episode (particularly depressive episode) recurrence. Psychosocial and environmental stressors are known to impact both the severity and course of illness, lengthening the time of recovery and increasing the risk of relapse.^{55;56}

1.4.3 Classification

Previously referred to as manic-depression, bipolar disorder is a mood disorder. It is differentiated from major depressive disorder by a history of mania or hypomania.²² Based on the presence of specific mood episodes, bipolar disorder has been divided into four subtypes: bipolar I; bipolar II; cyclothymic disorder; and bipolar disorder not otherwise specified.²² Further specifiers are used to describe the course of recurrent episodes, such as the pattern of episode occurrence and the longitudinal course of these episodes.²² Bipolar I disorder is characterized by the occurrence of one or more manic or mixed episodes.²² Bipolar II disorder is characterized by the occurrence of one or more major depressive episodes accompanied by at least one hypomanic episode.²² Cyclothymic disorder is characterized by the occurrence of numerous periods of depressive symptoms and of hypomanic symptoms in a two- year period, with no symptom-free period greater than two months in duration, and in the absence of a past history of a manic, mixed, or major depressive episode.²²

1.4.4 Course

Bipolar disorder is typically a lifelong disorder with an episodic and protean course. In bipolar I disorder, women typically first present with a depressive episode, whereas men present with a manic episode.²² Regardless of gender, the average age of onset for the first manic episode is 20 years.²² Patients rarely present with a first manic episode after the age of 40 years.²² Although a history of depression is not necessary to confirm a diagnosis of bipolar I disorder, more than 95 percent of patients experience at least one depressive episode.²² Psychotic symptoms can occur in both bipolar I and bipolar II disorder, although they are more common in bipolar I disorder.²² As stated, bipolar I disorder is an episodic condition with patients typically experiencing multiple episodes of mania and depression.²² Bipolar II disorder is also characterized by multiple

relapses or episodes.^{22;55} The duration and severity of these episodes, as well as the interval between episodes, varies by patient. Patients may experience normal functioning between episodes, but more than 50 percent experience some functional impairment after the onset of illness, with 10 to 15 percent experiencing severe impairment of function.^{55;56} Due to the prevalence of the disorder and the pervasiveness of associated symptoms, bipolar disorder is the sixth leading cause of disability in developed nations worldwide.⁵⁷ Bipolar disorder is also associated with an increased incidence of comorbidities including diabetes, substance misuse, anxiety, panic disorder and other mental disorders.^{18;22;58} These, combined with a lifetime prevalence of suicide of approximately 10 to 15 percent, contribute to an increased mortality rate in these patients.²²

1.4.5 Treatment

The goals of treatment include resolution of bipolar symptoms and prevention of further relapse while minimizing the risk of adverse effects. The management of bipolar disorder includes pharmacological and non-pharmacological strategies. It is estimated that only one-third of patients with bipolar disorder receive appropriate treatment.⁵⁹ This is due to a combination of factors including inadequate rates of diagnosis and high medication nonadherence rates due to lack of insight or medication intolerance.^{59;60} This section provides information on the role of pharmacotherapy in the acute and maintenance management of mania and depression. Particular emphasis will be given to the role of the second-generation antipsychotic agents.

1.4.5.1 Acute Affective Episodes: Mania

The American Psychiatric Association advocates the combined use of lithium and an antipsychotic, or valproate and an antipsychotic, as first-line

therapy for acute manic or mixed episodes.⁵⁵ In patients who are less ill, monotherapy with lithium, valproate or an antipsychotic are considered to be possibly sufficient. Alternative treatment options include use of carbamazepine or oxcarbazepine in lieu of lithium or valproate. The specific role of the aforementioned agents in the management of acute mania will now be presented.

1.4.5.1.1 Lithium

Lithium is the gold standard in the management of bipolar disorder and is indicated as both acute and prophylactic treatment.^{55;61} In placebo-controlled trials, 70 percent of patients treated with lithium experienced at least a partial reduction of acute mania or hypomania.⁶¹ In comparison trials, lithium monotherapy has been found to be more effective than carbamazepine or antipsychotics, but comparable in efficacy to valproate.⁶¹ Certain subsets of patients are thought to be less responsive to lithium including patients with rapid-cycling, mania secondary to a medical condition, and those with mania and mixed or dysphoric features.⁶¹ The use of lithium is complicated by its adverse effects profile, and the need for drug serum level monitoring, with up to 75 percent of patients experiencing some side effects.^{55;56} Adverse effects include: hypothyroidism; polyuria; polydipsia; weight gain; cognitive problems; sedation; lethargy; gastrointestinal toxicity; hair loss; and acne.^{55;56}

1.4.5.1.2 Anticonvulsant Agents

Also known as mood-stabilizing agents, the efficacy of the two most commonly used anticonvulsant agents, divalproex sodium (including its alternate formulations: sodium valproate and valproic acid) and carbamazepine, is well documented in acute bipolar mania.^{55;61} Both carbamazepine and divalproex are associated with considerable adverse effects burdens. Transient dose-related toxicities associated with carbamazepine include: neurological symptoms such as diplopia; blurred vision; fatigue; and ataxia.^{55;56} Less frequently, patients may

experience skin rashes, hyponatremia and weight gain. Infrequent serious toxicities include: blood dyscrasias; Stevens-Johnson syndrome; liver failure; and pancreatitis.⁵⁶ Routine serum drug level monitoring is required with carbamazepine because of its narrow therapeutic window.⁵⁵ Further complicating the use of carbamazepine is its action as an inducer of, and substrate for, cytochrome P 450, and hence the potential for multiple drug-drug interactions.⁵⁵ Adverse effects associated with valproate include: sedation; gastrointestinal distress; osteoporosis; polycystic ovarian syndrome; tremor; alopecia, increased appetite; and weight gain.^{55;56} Rare serious adverse effects include blood dyscrasias and hepatotoxicity, which can progress to liver failure.^{55;56} Both carbamazepine and divalproex are known teratogens.⁵⁵ Other possible agents in this category include: lamotrigine (for bipolar depression), and oxcarbazepine, although the evidence to support their use is limited.^{55;61}

1.4.5.1.3 Antipsychotics

The use of antipsychotics in the management of bipolar mania is common, and endorsed by several expert consensus series.^{21;62;63} This is due to a combination of factors including: limited efficacy of lithium and the anticonvulsant agents as monotherapy in certain subtypes; a prevalence of psychosis in 50 to 75 percent of patients with acute mania; and documented efficacy of the antipsychotics as mono- or adjunctive therapy.⁶⁴ Prior to the widespread availability of the second-generation agents, the use of the first-generation antipsychotics was commonplace. In a meta-analysis of 16 studies, including 2,738 patients with bipolar disorder, 84.7 percent received a first-generation antipsychotic, with monotherapy accounting for 53.8 percent of this use, and dual therapy with lithium, valproate or carbamazepine accounting for 47.4 percent of the use.⁶² In a study of hospitalized patients with bipolar I disorder published in 2001, antipsychotic agents were prescribed to 74 to 78

percent of patients with psychotic features, and to 33 to 41 percent without, with second-generation antipsychotics accounting for two-thirds of this use.⁶⁵ The role of the first- and second-generation antipsychotic agents in the acute management of bipolar mania will now be reviewed.

1.4.5.1.3.1 First-Generation Antipsychotics

Antipsychotics have been used in the acute management of bipolar mania since the 1950s.⁶⁴ Initially used to control agitation, these agents were subsequently noted to have anti-manic properties, and although less efficacious than lithium, have the advantage of a more rapid onset of action.⁶² If an antipsychotic agent is required, the second-generation antipsychotics are now preferred due to the unfavorable adverse effects profile associated with the first-generation agents.^{55;63} These include neuroleptic malignant syndrome, and extrapyramidal side-effects.^{55;64} In particular, patients with bipolar disorder have an apparent increased susceptibility to extrapyramidal side-effects and tardive dyskinesia. A prevalence of tardive dyskinesia of 19 to 41 percent has been noted in bipolar patients treated with the first-generation antipsychotics.⁶⁶

1.4.5.1.3.2 Second-Generation Antipsychotics

The efficacy of aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone in the management of acute mania has been documented in a number of large double-blind, placebo-controlled trials.⁶⁷⁻⁷⁴ When compared to placebo, an incremental response of 20 to 25 percent in the reduction of acute mania was typically seen.⁷⁵ When used as monotherapy, olanzapine, quetiapine and risperidone have been demonstrated to have comparable efficacy to lithium or haloperidol.⁷⁵ Similarly, olanzapine has been demonstrated to be comparable to,⁷⁶ or superior to,⁷⁷ divalproex monotherapy for the remission of acute mania. The efficacy of olanzapine, risperidone and quetiapine as adjunctive therapy to

lithium or divalproex has also been demonstrated, with an increase in response rate of approximately 20 percent seen with the combination therapy.⁷⁸⁻⁸¹

Olanzapine was first licensed as monotherapy for acute bipolar mania in September 2000.³⁷ It was subsequently licensed for use as adjunctive therapy with lithium or divalproex in acute mania in July 2003, and as maintenance monotherapy in January 2004.³⁷ Quetiapine and risperidone were newly approved in January 2004 and December 2003, respectively, for use as monotherapy and as adjunctive therapy with lithium or divalproex in the treatment of acute bipolar mania.^{38;39} Food and Drug Administration (FDA) approval for the use of aripiprazole and ziprasidone in acute manic and mixed episodes associated with bipolar disorder, with or without psychotic features was granted in September 2004 and August 2004, respectively.^{35;40}

There is evidence that clozapine is effective in bipolar disorder, including treatment-resistant cases. The use of clozapine is limited due to its adverse effects profile, in particular the risk of potentially fatal agranulocytosis.⁵⁰ When used in bipolar disorder, and consistent with the findings in schizophrenia, there are a number of adverse effects commonly associated with the use of the other second-generation antipsychotic agents. These include: extrapyramidal side-effects and tardive dyskinesia; endocrine disturbances such as hyperprolactinemia; weight gain; and metabolic disturbances such as dyslipidemia and diabetes. To be effective, a drug must be taken as prescribed; therefore, tolerability is critical to the success of treatment.

1.4.5.2 Acute Affective Episodes: Depression

As noted, the American Psychiatric Association advocates the combined use of lithium and an antipsychotic, or valproate and an antipsychotic, as first-line therapy for acute manic or mixed episodes.⁵⁵ While new data is emerging on the treatment of bipolar depression, historically few randomized clinical trials

have been conducted in this area.^{82;83} Controversy exists as to the risks and benefits of using antidepressants due to the potential for treatment-emergent mania.⁸³ Recent trials have highlighted the benefits of lamotrigine both as acute management, and for prevention of bipolar depressive episodes.⁸² When combined with lithium or divalproex, paroxetine has also been shown to have a significant antidepressant effect with limited risk of treatment-emergent mania.⁸² The potential for treatment-emergent mania with tricyclic antidepressant therapy has, however, been substantiated and would appear to limit the utility of these agents for bipolar depression.⁸²

The first-generation antipsychotics appear to be ineffective as antidepressants, and may, in fact, induce depressive symptoms in patients with bipolar depression.⁶⁴ In contrast, consistent with their effects as serotonin receptor antagonists, the second-generation antipsychotics appear to alleviate symptoms of acute depression in bipolar disorder, although the evidence is limited. In a randomized, double-blind clinical trial, olanzapine as monotherapy, or in combination with fluoxetine, was demonstrated to be superior to placebo in decreasing depressive symptoms in patients with bipolar disorder, while not increasing the risk of treatment-emergent mania.⁶⁸ A combined olanzapine / fluoxetine preparation has recently been licensed for this indication.⁸⁴ In a randomized placebo-controlled trial, quetiapine monotherapy was shown to be effective in the acute management of bipolar depression (including significantly reducing suicidal ideation) and to have a larger effect size compared to that recorded in similar placebo-controlled trials for olanzapine, and olanzapine-fluoxetine combination.⁸⁵ As with schizophrenia and bipolar mania, a careful risk/benefit analysis is warranted for each patient to balance the apparent benefits of therapy with the potential for adverse effects including: weight gain; diabetes;

hyperlipidemia; hyperprolactinemia; cardiac effects; and extrapyramidal side-effects.

1.4.5.3 Summary

The efficacy of lithium, the anticonvulsant agent's divalproex and carbamazepine, and the first-generation antipsychotics in acute bipolar mania is well established. There is also limited evidence to support the efficacy of the selective serotonin reuptake inhibitors (SSRIs) for bipolar depression. More recently, a number of the second-generation antipsychotics have emerged as effective treatment for both bipolar mania and depression. Despite these successes, up to 50 percent of patients with acute affective episodes do not respond to any of these agents. Furthermore, the use of these agents is complicated by unwanted side-effects, some of which can be serious.

1.4.5.4 Maintenance Phase Management

The goals of maintenance phase management include: relapse prevention; reduction of the risk of cycling frequency; mood instability and suicide; and improvement in psychosocial functioning.⁵⁵ Following the remission of an acute manic episode, maintenance therapy with a mood stabilizer is recommended while adjunctive treatments are tapered and discontinued.⁵⁵ While there is dispute as to what constitutes recovery from an acute episode, the maintenance phase is typically defined as the time interval from the recovery from one acute episode to the time of onset of a new acute episode.⁸⁶ Lifetime prophylaxis with a mood stabilizer is recommended for patients with bipolar I disorder that have experienced two manic episodes, or one severe episode.⁵⁵ Patients with bipolar II disorder are recommended to remain on lifelong therapy if they experience three hypomanic attacks, or require an antidepressant but become hypomanic.⁵⁵ The use of lithium, anticonvulsants and antipsychotics in the maintenance phase management of bipolar disorder will now be discussed briefly.

1.4.5.4.1 Lithium

Although early studies reported lithium to be more effective than placebo in preventing episode recurrence, many of these studies were methodologically flawed.^{55;82;86} More recently, naturalistic studies have indicated that lithium decreases the risk of relapse in approximately one-third of patients, although these studies were characterized by high drop-out rates.⁸⁶ Two recent randomized controlled trials have confirmed the efficacy of lithium compared to placebo in relapse prevention.⁸² Specifically, lithium reduced the risk of recurrence of mania, but not depression, when compared to placebo.⁸² Lithium has demonstrated possibly specific anti-suicide effects, and is the only maintenance treatment proven to decrease the risk of suicide in patients with bipolar disorder.⁸⁷ Lithium is less effective in certain patient subsets, including those with rapid cycling.⁵⁵ Whereas lithium appears to be more effective at higher serum drug levels, the corollary is poorer tolerability.⁵⁵ Nonadherence to therapy is common, particularly during maintenance therapy. In addition to the risk of relapse, abrupt discontinuation of lithium may increase the risk of a treatment-refractory state thereby limiting the benefit of future treatment. Forty percent of acute patients are believed to be resistant to lithium.⁸⁸

1.4.5.4.2 Anticonvulsants

Lamotrigine is the only anticonvulsant agent approved by the FDA for maintenance treatment in bipolar disorder.⁵⁵ It is well-tolerated, with headache the most commonly reported side-effect in clinical trials.⁵⁶ No serum drug level monitoring is required and it appears to have no effect on weight or cognition.⁵⁵ Limited data with divalproex shows that it appears to be at least comparable in efficacy to lithium as a maintenance agent.⁵⁵ Currently there is no conclusive evidence to support the use of oxcarbazepine, carbamazepine, topiramate or gabapentin as maintenance therapy.^{55;89}

1.4.5.4.3 Antipsychotics

The first-generation antipsychotics have not been demonstrated to be effective in the long-term treatment of bipolar disorder.⁷⁵ Although effective as anti-manic agents, they have not been demonstrated to prevent depression, and moreover, may contribute to its development.⁷⁵ As noted previously, the use of these agents in bipolar disorder is complicated by their adverse effects profile, in particular the propensity to cause tardive dyskinesia.⁶⁶

Limited data support the long-term use of the second-generation antipsychotics. Olanzapine, the only agent in this class approved for this indication, was licensed as maintenance monotherapy in January 2004.³⁷ When used as monotherapy, it has been shown to be significantly more effective than placebo in preventing manic and depressive relapses.⁹⁰ Similarly, when used as monotherapy, or in combination with lithium or divalproex, it has also been demonstrated to be significantly superior to monotherapy with lithium or divalproex in preventing manic, although not depressive relapse.^{75;91} There is preliminary evidence for the efficacy of the other second-generation antipsychotics as maintenance therapy; however, the results of long term trials are pending.⁷⁵

Although olanzapine has demonstrated efficacy as maintenance monotherapy for relapse prevention in bipolar disorder, some results from the clinical trials highlight key issues relating to the long-term management of bipolar disorder. The studies were characterized by high rates of treatment discontinuation, with 52-week completion rates of 23.6 to 46.5 percent for olanzapine, 9.6 percent for placebo, and 32.7 percent for lithium.⁷⁵ Although patients experienced a significant reduction in the risk of affective relapse, relapse rates in patients on monotherapy were still considerable, that is, from 30 to 46.7 percent with olanzapine compared to 80.1 percent with placebo, and 39

percent with lithium.⁷⁵ Due to its variable course and considerable interpatient variability, bipolar disorder is difficult to manage. As seen here, it is characterized by high rates of treatment non-adherence and poor persistence with therapy, which may reflect limited efficacy or poor tolerance of therapy. In tandem with efficacy research, it is important to study the long-term tolerability of these agents, so that the optimal agent can be selected for each patient.

1.4.6 Summary

Bipolar disorder is a prevalent condition characterized by multiple relapses and a variable course. The majority of patients do not respond adequately to monotherapy. Long-term maintenance therapy is required to ameliorate symptoms and prevent relapse. Antipsychotic agents are now widely used in the acute and long-term management of bipolar disorder. In particular, the second-generation antipsychotic agents have been endorsed for use as both mono- and adjunctive therapy, in patients with and without psychotic symptoms. The use of these agents is likely to expand following their recent FDA approval for these indications. The acute and long-term risks associated with these agents, including the potential for treatment-emergent diabetes, needs to be determined so that their role in the management of bipolar disorder can be more fully assessed.

1.5 Section 3: General Background on other Psychotic Disorders

In addition to schizophrenia, there are a number of other disorders classified as being psychotic disorders. While all include psychotic symptoms as a prominent feature, they differ in their etiology, the duration of symptoms and the constellation of symptoms encompassed by the term ‘psychotic.’²² Disorders for which psychotic symptoms are present as associated, rather than prominent features, of the disorder are usually categorized according to the major diagnosis.²² The presence of psychosis is then included as a specifier, for example, major depressive disorder, with psychotic features.²² In addition to defining psychosis, this section will provide background information on the various psychotic disorders as well as conditions in which psychotic symptoms commonly occur. The role of the second-generation antipsychotics in the management of these disorders will then be discussed.

1.5.1 Definition of Psychosis

The term psychotic has historically had a number of definitions, the most restrictive of which is the occurrence of delusions or prominent hallucinations in the absence of insight.²² Although the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, (DSM IV) limits the definition of psychosis to the presence of certain symptoms, these vary according to the diagnostic category.²² For example, in schizophrenia, schizoaffective disorder, schizophreniform disorder and brief psychotic disorder, the term ‘psychotic’ refers to the presence of delusions, prominent hallucinations, disorganized speech, or grossly disorganized or catatonic behavior.²² Psychosis in the context of delusional disorder, or shared psychotic disorder, refers only to a patient being delusional.²²

1.5.2 Classification (DSM IV Criteria)

Included in the DSM IV section entitled ‘Schizophrenia and Other Psychotic Disorders’ are the following disorders: schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance-induced psychotic disorder; and psychotic disorder not otherwise specified.²² As noted, psychotic symptoms may accompany a variety of medical conditions. In this case, they are considered to be associated, rather than prominent features of the disorder, for example, psychoses associated with major depressive disorder.

1.5.3 Epidemiology and Course

A brief description of these psychotic disorders will be provided here, focusing on their epidemiology and course. In particular, those features that differentiate these disorders from schizophrenia are highlighted.

1.5.3.1 Schizophreniform Disorder

This disorder is indistinguishable from schizophrenia with the exception of two features: duration and impairment of function. Whereas schizophrenia must persist in excess of six months, with a minimum of one month of active-phase (two or more symptoms), schizophreniform disorder is defined as a disorder that persists for one month, but no longer than six months.²² In addition, schizophrenia is characterized by functional impairment in at least one domain whereas no such impairment is required in schizophreniform disorder.²² The prevalence of schizophreniform disorder is estimated to be one-fifth of that of schizophrenia.²² Prospectively, in a clinical setting, a diagnosis of schizophreniform disorder is a provisional diagnosis, with approximately one-third of patients experiencing symptom remission within six months and,

therefore, meeting the criteria for the disorder and the remainder proceeding to being diagnosed as having schizophrenia or schizoaffective disorder.²²

1.5.3.2 Schizoaffective Disorder

This disorder is characterized as a combination of a mood disorder and symptoms characteristic of schizophrenia.²² To fulfill the diagnosis, mood symptoms must be present for a considerable proportion of the entire duration of illness but in addition there must be a minimum two-week period of illness where the patient has psychotic symptoms in the absence of prominent mood symptoms.²² The prevalence of schizoaffective disorder is unknown, but it is apparently less common than schizophrenia. Differentiating between schizophrenia, schizoaffective disorder and mood disorders with psychotic features can be difficult, and frequently a diagnosis may change according to the prominent symptoms within an episode or in subsequent episodes.²²

1.5.3.3 Brief Psychotic Disorder

This disorder differs from schizophrenia in two regards: the duration of psychosis is shorter, with a minimum duration of at least one day but not exceeding one month; and the patient must experience full recovery to premorbid functioning.²² The prevalence of this disorder is unknown.²² Brief episodes of psychosis may occur with a wide range of medical conditions and in addition, the condition may be difficult to differentiate from schizophreniform disorder if the symptoms remit in less than one month in response to antipsychotic treatment.²²

1.5.3.4 Delusional Disorder

Delusional disorder is distinguished from schizophrenia in that the symptoms are generally limited to delusions, and do not include other psychotic symptoms.²² It may be difficult to differentiate from other disorders for which delusions are a prominent symptom.²² Delusional disorder usually manifests late

in life, has a variable course, affects men and women equally, and has an estimated population prevalence of 0.03 percent.²²

1.5.3.5 Shared Psychotic Disorder

This is a delusional disorder characterized by the co-occurrence of delusions in an individual under the influence of another who has a pre-existing psychotic disorder featuring delusions as a prominent symptom.²² While the condition is typically chronic, it remits over time when the patient is separated from the primary case.²² The prevalence of this disorder is unknown, with a belief that the condition is under-diagnosed.²²

1.5.3.6 Psychotic Disorder Due to a General Medical Condition

Psychotic symptoms assessed as being a direct physiological consequence of a general medical condition are included in this disorder.²² Patients are subdivided according to their predominant symptoms: delusions or hallucinations.²² The prevalence, course and management of the disorder depend on the underlying etiology, with psychotic symptoms generally remitting with treatment of the underlying condition.²²

1.5.3.7 Substance-Induced Psychotic Disorder

In this disorder, psychotic symptoms are judged to be a direct physiological consequence of an ingested substance (alcohol, drug of abuse, medication or toxin).²² Patients are subtyped according to their predominant symptom: delusions or hallucinations; with additional specifiers used to indicate the time of onset of the symptoms, that is, during intoxication or during substance withdrawal.²² Psychotic symptoms typically remit on withdrawal of the substance, or within weeks in the case of withdrawal syndrome. A differential diagnosis may be difficult where there are comorbid medical conditions.²²

1.5.3.8 Psychoses not otherwise Specified

This diagnosis is assigned when the presenting psychotic symptoms do not meet the criteria for any of the specific psychotic disorders, or if there is inadequate information to concur or contradict with another diagnosis.²²

1.5.3.9 Major Depressive Disorder with Psychotic Features

Major depressive disorder is classified according to severity, with severe episodes categorized as being with, or without psychotic episodes.²² Psychotic symptoms include delusions or hallucinations (which are typically auditory), the content of which are usually consistent with the depressed mood (i.e., mood congruent).²² The prevalence of psychotic depression is estimated to be 0.6 percent in the general population, accounting for approximately 20 percent of major depressive episodes.⁹² Psychotic depression is associated with greater morbidity and mortality than non-psychotic depression, and is associated with an increased risk of relapse and recurrence, although the literature supporting this is equivocal.⁹³ Psychotic depression may be difficult to distinguish from other conditions where psychoses and depression co-occur including schizophrenia, delusional disorder and psychotic disorder not otherwise specified.²²

1.5.4 Role of the Second-Generation Antipsychotics

With the exception of clozapine, which has a licensed indication for reduction of suicidal ideation in patients with schizoaffective disorder, the second-generation antipsychotics are not licensed for use in conditions other than schizophrenia and bipolar mania. (Table 1.1).³⁵⁻³⁹ However, there is widespread clinical consensus that these medications are appropriate for the management of psychoses regardless of the etiology. In an expert consensus guideline series entitled ‘Optimizing Pharmacological Treatment of Psychotic Disorders,’ the role of these agents was considered for patients with psychotic disorders.⁹⁴ Psychotic

disorders were defined as those included in the DSM IV criteria discussed above, that is, schizophrenia; schizoaffective disorder; schizophreniform disorder; delusional disorder; and brief psychotic disorder.⁹⁴ No adjustment to treatment was recommended based on the etiology of the psychosis, rather modifications were proposed based on the patient experiencing first-episode versus multiple recurrent episodes of psychoses, and based on the presence of comorbid disease states.⁹⁴ In a similar guideline examining the use of antipsychotics in older patients, the experts concurred that the use of antipsychotics was appropriate in patients with psychosis regardless of etiology.¹¹

Treatment recommendations for psychoses associated with major depressive disorder include the use of electroconvulsive therapy (ECT) or a combination of antidepressant and an antipsychotic, although monotherapy with the second-generation antipsychotics olanzapine and risperidone has also been used.⁹⁵⁻⁹⁸ In particular, combined treatment with olanzapine and fluoxetine has been compared to olanzapine monotherapy, and placebo in the treatment of major depressive disorder with psychotic features.⁹⁹ Combined therapy was associated with a significantly higher response rate than with either olanzapine monotherapy ($p=0.027$) or placebo ($p=0.004$), although this finding was not corroborated in a subsequent trial.⁹⁹

The key difference between the use of antipsychotics for schizophrenia and non-schizophrenia conditions appear to be the dose and duration of therapy, with typically lower doses recommended for conditions other than schizophrenia. Schizophrenia is characterized as a life-long chronic relapsing condition.²⁶ It is, therefore, recommended that antipsychotics be continued indefinitely at the lowest effective dose to prevent relapse.^{11;94} In fact, the majority of experts in the field would not lower the dose of antipsychotic in the maintenance phase from that required in the acute treatment phase.⁹⁴ Those who endorse the strategy of

using a lower maintenance phase dose recommend that the patient be stable for a period of six months, and preferably one year prior to attempting a dose reduction.⁹⁴ In contrast, a shorter treatment duration is recommended in other conditions.¹¹ The duration of treatment recommended before an attempt is made to discontinue treatment, ranges from one week to six months. (Table 1.2)¹¹

Table 1.2: Recommended Duration of Treatment (after a Clinical Response Achieved) with an Antipsychotic Prior to Attempting to Discontinue Treatment, Stratified According to Treatment Indication¹¹

Condition	Duration and Action
Delirium	1 week
Agitated Dementia (with and without delusions)	Begin taper in 3-6 months to determine lowest effective maintenance dose
Schizophrenia	Indefinitely at lowest effective dose
Delusional Disorder	6 months to indefinitely at the lowest effective dose
Psychotic Major Depression	6 months
Agitated Non-Psychotic Major Depression	2 months
Non-Psychotic Major Depression with Severe Anxiety*	2 months
Mania with Psychosis	3 months
Mania without Psychosis	2 months

* Approximately 33 percent of experts did not advocate the use of antipsychotics for this condition other than for patients that were intolerant or, or unresponsive to first-line treatment.

1.5.5 Summary

In this section, psychotic disorders other than schizophrenia, as well as disorders for which psychotic symptoms may present as associated symptoms were outlined. A number of these disorders are clinically very similar to schizophrenia and may be considered as ‘schizophrenia spectrum disorders.’²² Specifically, schizophreniform disorder is indistinguishable from schizophrenia with the exception of the duration of the disorder. Schizoaffective disorder also

may be difficult to distinguish from schizophrenia and the patient diagnosis may change according to the prominent symptoms during a given episode. The use of antipsychotics, including the use of the second-generation antipsychotics, is considered clinically acceptable for psychotic conditions despite the fact that they do not have licensed indications for such use. However, the pattern of antipsychotic use in conditions other than schizophrenia appears to vary from that in schizophrenia, with typically lower doses or shorter durations of treatment advocated.¹¹

1.6 Section 4: General Background on Dementia with an Emphasis on Behavioral and Psychological Disturbances of Dementia

The second-generation antipsychotics have been widely used in patients with behavioral and psychological symptoms of dementia, in part because of their favorable adverse-effects profile compared to the first-generation agents. While psychotic symptoms are not synonymous with dementia, there is a high life-time prevalence of psychoses in patients with dementia. The use of second-generation antipsychotics for both psychotic and non-psychotic symptoms of dementia is reviewed in this section.

1.6.1 Classification (DSM IV Criteria)

According to the DSM IV, patients with psychoses that is considered to be “a direct etiological consequence of the pathological process causing the dementia” may be classified as having a diagnosis of a psychotic disorder due to a general medical condition, in addition to having a diagnosis of dementia.

1.6.2 Epidemiology and Course

Dementia, which was previously categorized under the now defunct term ‘organic mental disorder,’ is considered primarily to be a cognitive disorder characterized by multiple cognitive deficits.²² Dementias are categorized according to presumed etiology and include: Dementia of Alzheimer’s type; Vascular dementia; Dementia due to other general medical conditions (including Parkinson’s disease and Huntington’s disease); Substance-induced persisting dementia; Dementia due to multiple etiologies; and Dementia not otherwise specified.²² The prevalence of dementia increases with age, with a prevalence of 1.4 to 1.6 percent in those aged between 65 to 69 years, increasing to 16 to 25 percent in those aged over 85 years.²² Alzheimer’s disease is the most common of the dementias accounting for approximately 50 to 75 percent of all cases.¹⁰⁰

Vascular dementia is the next most common form of dementia, although the prevalence of this condition is unknown.¹⁰⁰ Behavioral (agitation, physical and verbal aggression, noisy vocalizations) and psychological (delusions and hallucinations) symptoms are common in elderly patients with dementia and are usually grouped under the umbrella term ‘behavioral and psychological symptoms of dementia’ (BPSD).¹⁰¹ The lifetime prevalence of these symptoms in patients with dementia is estimated to be 50 to 70 percent in those with Alzheimer’s disease, and between 70 to 80 percent in those with any type of dementia.^{101;102} In particular, psychotic symptoms are common in patients with dementia secondary to Parkinson’s disease, Lewy body disease, Pick’s disease and the other frontal lobe dementias.¹⁰⁰ The typically late-life onset of dementia facilitates its differential diagnosis from other conditions associated with cognitive impairment.²² What can be difficult however is distinguishing between delirium (a reversible condition) and dementia, particularly as delirium may often be superimposed on a preexisting dementia.²²

1.6.3 Role of the Second-Generation Antipsychotics

Treatment options for BPSD have traditionally included mechanical restraints.¹⁰⁰ These are generally no longer favored as an increased level of agitation has been documented in restrained patients.¹⁰⁰ Similarly, first-generation antipsychotics which are effective, and previously widely used, are now considered second-line due to their unfavorable adverse effects profile, particularly the potential for extrapyramidal side-effects.¹⁰⁰⁻¹⁰² The second-generation agents are thought to be more effective in managing psychosis and aggression than the first-generation agents and have the additional benefits of a decreased potential for extra-pyramidal side-effects and efficacy at relatively low doses.^{101;102} It is generally recommended that elderly patients be started at approximately 25 percent of the usual antipsychotic dose due to a possible

altered rate of metabolism of these agents, decreased tolerance of adverse effects and an increased likelihood of comorbid conditions.¹⁰² Gradual titration of the dose to effect is also recommended to minimize adverse effects such as orthostatic hypotension and sedation.¹⁰²

Although not approved by the FDA for this indication, there is a general clinical consensus that the use of second-generation antipsychotics for the management of psychotic symptoms in patients with dementia is appropriate.^{11;100} Their use for this indication is widespread and well documented.¹⁰¹⁻¹⁰³ The role of these agents for behavioral disturbances, including agitation, is less clear. As noted, symptoms are frequently grouped under the umbrella term BPSD, therefore, it may be difficult to ascertain the extent to which these agents are being used for psychotic symptoms, as opposed to behavioral disturbances.¹⁰¹ Due to the pervasive use of antipsychotics in patients with dementia, particularly among nursing-home residents, and a perception that these agents were being over-used, the Centers for Medicare and Medicaid Services issued guidelines on what was considered appropriate use of antipsychotics in nursing homes.^{103;104} They recommended that antipsychotic therapy be limited to the following indications: psychotic disorders, Tourette's syndrome, Huntington's syndrome, or if hallucinations are currently present.¹⁰⁴ In addition, the use of antipsychotics could be considered in 'high risk' patients, that is, those with cognitive impairment exhibiting verbally or physically abusive behavior, or socially inappropriate /disruptive behavior, provided this was currently being monitored.¹⁰⁴ Similarly, in an expert consensus guideline series, the use of antipsychotics was usually considered to be indicated in dementia patients with agitation and delusions, but only sometimes indicated in dementia patients with agitation only.¹¹ Of note, however, is a black box warning issued in April 2005, by the Center for Drug Evaluation and Research highlighting an

increased rate of death in elderly patients with dementia-related psychosis treated with a second-generation antipsychotic compared to placebo. This was based on analyses of seventeen placebo-controlled trials in which the rate of death among treated patients was 1.6 to 1.7 fold higher than for the placebo group (4.5% vs. 2.9%, respectively).¹⁰⁵

The majority of the literature supporting the use of the second-generation antipsychotics for BPSD relate to the use of risperidone,¹⁰² the efficacy of which has been demonstrated in a number of randomized, controlled trials.^{106;107} In a controlled study of dementia patients (N=625) residing in a nursing home or chronic hospital, a clinically significant improvement in psychotic symptoms was documented with risperidone at a dose of one milligram daily ($p=0.02$), with slightly higher efficacy at a dose of two milligrams daily ($p=0.002$).¹⁰⁶ Increased adverse effects with the two milligram dose prompted the authors to recommend the lower dose in this cohort.¹⁰⁶ In a similar trial of 344 nursing home patients with dementia, risperidone at a mean dose of 1.1 milligram daily was found to be well tolerated and efficacious in decreasing BPSD.¹⁰⁷ The efficacy of olanzapine in the treatment of BPSD was documented in a randomized, controlled trial of 206 nursing home residents with Alzheimer's disease. A significant improvement in psychotic symptoms was noted at doses of five to ten milligrams daily, with the five milligram dose proving most beneficial.¹⁰⁸ There is limited evidence to support the use of quetiapine in patients with dementia-related psychoses, although preliminary reports from small open-label studies suggest that it is well-tolerated and associated with an improvement in symptoms at an average dose of 60 to 100 milligrams daily.¹⁰⁹⁻¹¹¹

The use of second-generation antipsychotics is widespread in patients with BPSD. In a large, retrospective study of nursing home residents in the U.S. in 1999 to 2000, 18.2 percent of patients were receiving an antipsychotic with

second-generation antipsychotics accounting for approximately 60 percent of this use.¹⁰³ Likewise, in a study of patients with dementia discharged from psychiatric inpatient units, 36.6 percent were receiving antipsychotic therapy.¹⁰¹ The dose of antipsychotic used is considerably lower than that seen in conditions such as schizophrenia, moreover, the dose required to treat behavioral disturbances of dementia may be lower than that required for psychotic symptoms in dementia. In a 12-week randomized, controlled trial, risperidone at a dose of 0.5-2.0 milligrams daily was effective for behavioral symptoms, compared to a dose of 1.0-2.0 milligrams daily in those with psychotic symptoms.¹⁰⁶

As noted in section three, shorter periods of treatment are advocated when antipsychotics are used for conditions other than schizophrenia. Regardless of the presence of absence of delusions, it is generally recommended that an attempt to taper treatment to the lowest effective dose or to discontinuation be made within three to six months in patients with agitated dementia (Table 1.2).¹¹

1.6.4 Summary

This section reviewed the use of second-generation antipsychotics in patients with dementia. For patients with psychotic symptoms associated with dementia, the use of these agents is considered clinically acceptable despite the fact that they are not licensed for such use. The role of antipsychotics in the management of behavioral symptoms of dementia is less well established. In retrospective studies, it may however be difficult to distinguish between appropriate and inappropriate use of these medications because symptoms are commonly grouped under the term BPSD.¹⁰¹ Likewise, clinical trials in this cohort may not distinguish between behavioral and psychological symptoms for the purpose of trial inclusion. Similar to the other non-schizophrenia conditions, the pattern of antipsychotic use differs from that in schizophrenia, with lower doses used and shorter durations of treatment advocated.

1.7 Section 5: General Background on Non-Psychotic Mental Disorders

1.7.1 Introduction

The second-generation antipsychotics have been used in a wide range of mental disorders in addition to being used to treat schizophrenia, bipolar disorder and other psychotic conditions. The purpose of this section is to provide some background material on this diverse range of conditions and to highlight the role of the second-generation antipsychotics in their management.

1.7.1.1 Post Traumatic Stress Disorder

Post traumatic stress disorder (PTSD) is categorized as an anxiety disorder and has an estimated life-time prevalence of 7.8 percent, although a prevalence as high as 20 percent has been noted in at-risk populations.^{22;112} The DSM IV defines PTSD as the development of a characteristic set of symptoms that persists for more than one month subsequent to a traumatic experience and that cause significant distress or functional impairment.¹¹³ Cognitive behavioral therapy and SSRIs are established effective treatment for PTSD.¹¹³ Currently the only FDA-approved treatments for PTSD are sertraline and paroxetine.¹¹⁴ Guidelines on the use of other pharmacological agents depend on specific target symptoms that the patient experiences. In particular, the use of second-generation antipsychotics has been recommended for psychosis, psychotic depression and mania secondary to PTSD as well as refractory PTSD.¹¹² There is preliminary evidence to support the use of clozapine, olanzapine, quetiapine and risperidone in the management of PTSD.¹¹⁴⁻¹¹⁷

In an uncontrolled eight-week study, 48 patients with combat-induced PTSD were treated with olanzapine monotherapy (mean dose: 14 milligrams). A significant improvement in all symptoms was noted; however, over one-third of

patients failed to complete the trial primarily due to intolerable adverse effects.¹¹⁶ Risperidone at a mean daily dose range of 1-3 milligrams has been noted to be effective in reducing target symptoms of combat-induced PTSD in a number of small trials.¹¹⁵ Likewise, in a six-week open label add-on trial of 20 combat veterans with PTSD who had an inadequate response to antidepressant therapy, quetiapine was shown to be effective in ameliorating PTSD symptoms at a mean daily dose of 100 milligrams (SD: 70).¹¹⁴

1.7.1.2 Obsessive-Compulsive Disorder

As with PTSD, obsessive-compulsive disorder (OCD) is categorized as an anxiety disorder.²² Although the exact prevalence is unknown, it is estimated to range from 2.5 to 7.9 percent of the general population.^{22;118} The condition is commonly associated with Tourette's disorder, with an estimated comorbidity in five to seven percent of patients with OCD.²² The first-line treatment of patients is SSRI therapy, however between 40 to 60 percent of patients are poorly responsive to such therapy. Although there are few randomized, controlled trials to support their use, the second-generation antipsychotics have been widely used as augmentation therapy in this population. In a randomized, controlled trial, 36 patients with OCD refractory to a 12-week course of SSRI therapy were randomized to receive augmentation therapy with risperidone or placebo. Using a mean daily dose of 2.2 milligrams (SD: 0.7mg), significant reductions in obsessive-compulsive behavior ($p<0.001$), depression ($p<0.001$) and anxiety ($p=0.003$) were noted compared to placebo therapy. Similar findings were documented in a small, open-trial of risperidone augmented SSRI therapy.¹¹⁹ Likewise, olanzapine has been noted to be efficacious and well-tolerated in a small, placebo-controlled trial (N=26) using a final mean dose of 11.2 milligrams (SD: 6.5mg).¹²⁰

1.7.1.3 Borderline Personality Disorder

Borderline personality disorder (BPD) is a prevalent condition in the U.S., with an estimated prevalence of two percent in the general population.²² It is a challenging and expensive disorder to treat, with a prevalence of 10 percent in out-patient mental health clinics, and 15 to 20 percent in inpatient mental health beds.²² The disorder is characterized by marked instability of relationships and affect, impulsivity and recurrent suicidal behavior.²² Psychotic-like symptoms may occasionally be present.²² A wide range of medications have been studied for the management of BPD, but there is no standard approach to the management of this disorder.¹²¹ The second-generation antipsychotics have shown to be promising in the management of BPD, with preliminary evidence that they are effective in symptom reduction, particularly in reducing impulse-aggression.^{121;122} Support for the use of risperidone comes from two small trials using mean doses of 2.2 milligrams and 3.3 milligrams daily where a significant reduction in impulse aggression was noted.¹²² The efficacy of olanzapine has similarly been noted in two short-term, randomized, controlled trials using mean doses of olanzapine of 5.3 to 6.9 milligrams daily where significant improvement in BPD symptoms were noted.^{121;122} Likewise quetiapine and clozapine have preliminary evidence of efficacy at mean daily doses of 200 to 300 milligrams, and 334 milligrams, respectively.¹²² As long-term trials have yet to be conducted in this population, it is not known whether maintenance or intermittent therapy will prove superior, nor what the optimal doses for acute treatment and maintenance therapy are.¹²²

1.7.1.4 Autistic Disorder and other Pervasive Developmental Disorders

Autistic disorder is a neuropsychiatric disorder with an approximate prevalence of five cases per 100,000 individuals.²² Autistic disorder is a life-long developmental disorder defined by an age of onset less than three years and is the

most common of the pervasive developmental disorders.²² Although commonly associated with mental retardation, autism is distinct from it.²² Antipsychotic therapy has been used to manage some of the specific behavioral disturbances associated with autism, including self-injury, aggression and stereotypies.^{123;124} The first-generation antipsychotics have been widely used for this indication; however, their use is limited by the high incidence of treatment-induced dyskinesias in this population.¹²³

The majority of the literature regarding use of second-generation antipsychotics for autism relates to their use in children.^{123;124} Studies are typically small and restricted to case series and open-label non-randomized trials.^{123;124} Risperidone is the most widely studied agent with a median dose of 2.7 milligrams daily.¹²³ It has been demonstrated to be effective and well tolerated in a short-term, randomized, double-blind placebo-controlled trial of children with autism and serious behavioral problems.¹²⁵ In studies that restricted their inclusion to adults, the mean daily dose range was from 2.9 to 7.0 milligrams.^{123;124} In a randomized, controlled trial of 31 adults with autistic disorder and pervasive developmental disorder, risperidone at a mean daily dose of 2.9 milligrams (SD: 1.4mg) was seen to be well tolerated and effective in reducing the behavioral symptoms of autism.¹²⁶ The possible role of olanzapine in autism has been reported in a number of small studies, all of which included children with autism.¹²³ The median daily dose used was 7.8 milligrams daily (range 7.5 to 15mg), it was well tolerated and appeared to be effective although these findings need to be substantiated in larger, controlled trials.¹²³ There is also preliminary evidence to support the use of clozapine and quetiapine for this condition.¹²³

1.7.1.5 Major Depressive Disorder without Psychoses

Major depressive disorder is a prevalent condition in the U.S., affecting approximately ten percent of the population annually.⁹⁸ As outlined in section 3, severe episodes of major depressive disorder are further specified according to the presence or absence of psychotic symptoms.²² While the use of antipsychotic therapy for psychotic symptoms is generally accepted, the use for non-psychotic conditions is more contentious.¹¹ A number of studies have, however, examined the use of these agents for treatment-resistant depression. One definition of treatment-resistant depression is a failure to respond to an adequate dose and duration of at least two different antidepressant medications.⁹⁸ It is estimated that 46 to 50 percent of patients fail to respond, or achieve only partial response to conventional antidepressant treatment.^{98;127} In a 76-week, open-label study of adults with major depressive disorder (N=560), including a subset of patients with treatment-resistant depression (N=145), a combination of olanzapine and fluoxetine was tested.⁹⁸ The mean modal dose of olanzapine was 7.7 milligrams (SD: 3.9mg) daily for patients with treatment-resistant depression and 7.4 milligrams (SD: 3.3mg) daily for those with non-treatment-resistant depression.⁹⁸ Combination therapy was seen to be rapidly effective, tolerable, with a durable response in both groups.⁹⁸ The authors concluded that while effective in patients without treatment-resistant depression, it was unlikely to be necessary for the majority of such patients.⁹⁸ However, they concluded that combination therapy may represent a reasonable option for treatment-resistant depression, or in patients with severe acute major depressive disorder requiring a rapid response.⁹⁸ Similar rapid response has been seen in a number of small studies using risperidone and ziprasidone augmentation in patients with an inadequate response to SSRI therapy.^{127;128}

While second-generation antipsychotics are being used to treat non-psychotic depression, including treatment-resistant depression, it is generally advocated that their use be limited to patients that are refractory to other treatments including failing multiple different antidepressants and augmentation strategies such as lithium and thyroid therapy.⁹⁶ In an expert consensus guideline series examining the use of antipsychotics in older patients, there was limited support for the use of a second-generation antipsychotic in treatment-resistant depression, with only 36 percent responding that they would consider adding a second-generation antipsychotic, and a general recommendation that an attempt be made to discontinue treatment two months after a response had been noted (Table 1.2).¹¹

1.7.1.6 Other Conditions

The second-generation antipsychotics have been used in a wide range of conditions in addition to those enumerated above. These include: anorexia nervosa; substance abuse; behavioral disturbances associated with intellectual disability; delirium; and movement disorder.¹²⁹ The literature supporting their use for such indications is generally limited to anecdotal reports, case series, small open-label trials and rarely, controlled trials.¹²⁹ This does not appear to limit the use of antipsychotics for these indications in clinical practice. For example, the use of antipsychotics in institutionalized patients with intellectual disability is widespread, with reports that approximately 50 percent of patients are receiving antipsychotic treatment.¹³⁰ Despite this, there are few systematic controlled trials in this population and for those trials that have been conducted, equivocal findings regarding the efficacy of such treatment.¹³⁰

1.7.2 Summary

There are a wide variety of non-psychotic conditions for which the second-generation antipsychotics are commonly used in clinical practice. The pattern of antipsychotic use in a number of these conditions appears to differ from that for schizophrenia, particularly in terms of dose and duration of treatment. Moreover, these populations may differ from those with schizophrenia or bipolar disorder with respect to demographic variables and the occurrence, and treatment of comorbid conditions. This study seeks to examine the occurrence of new-onset diabetes associated with the second-generation antipsychotics, and in particular the differential rate of new-onset diabetes associated with the various agents. As will be discussed in section 8, the incidence of diabetes is known to vary according to demographic variables and comorbid clinical conditions. It is important to account for these differences, including any possible treatment-related differences, such as the potential for a dose-related effect, so that the association between second-generation antipsychotic use and new-onset diabetes can be more accurately described.

1.8 Section 6: Metabolic Disturbances Associated with the Second-Generation Antipsychotic Agents

The second-generation antipsychotic agents have been associated with a variety of metabolic disturbances, the most serious of which is glucose dysregulation. This includes the development of new-onset diabetes, diabetic ketoacidosis and hyperglycemic nonketonic coma, with infrequent fatalities reported. Weight gain is widely reported with a number of the second-generation antipsychotic agents. While it is disputed if this is the mechanism by which antipsychotics induce diabetes, obesity and weight gain are independently associated with an increase in morbidity and mortality. Additional metabolic adverse effects described with the second-generation antipsychotics include dyslipidemia, pancreatitis, and hyperprolactinemia. In this section, each of these metabolic disturbances is reviewed in detail, with particular emphasis on antipsychotic-induced glucose dysregulation.

1.8.1 Antipsychotic Induced Weight Gain

1.8.1.1 Magnitude of Weight Gain

A commonly documented adverse effect of the antipsychotic agents is weight gain. The extent of this gain appears to vary by drug. Allison et al. conducted a meta-analysis of estimated changes in weight, from baseline, after ten weeks of treatment with standard doses of second-generation antipsychotic agents.¹³¹ As illustrated in Table 1.3, the highest weight gain liabilities were noted with clozapine and olanzapine, with ziprasidone appearing to be weight neutral.¹³¹

Table 1.3: Estimated Weight Change (Kg) from Baseline at 10 Weeks in Patients Treated with Standard Doses of Second-Generation Antipsychotic Agents¹³¹

Antipsychotic	Estimated Weight Change (Kg) (95% CI)
Placebo	-0.74 (-1.60-0.12)
Clozapine	4.45 (3.02-5.88)
Olanzapine	4.15 (3.82-4.48)
Quetiapine*	2.18 (1.53-2.83)
Risperidone	2.10 (1.69-2.51)
Ziprasidone	0.04 (-0.49-0.57)

* Effect estimated at six weeks of treatment

The FDA defines a clinically significant weight gain as an increase of seven percent or more from baseline body weight, although this definition has not been universally adopted. Using this definition, Table 1.4 illustrates the percentage of patients experiencing clinically significant weight gain in short-term, randomized, placebo controlled trials of four to eight weeks duration.^{35;37-40} The relative ordering of the agents is consistent with the relative ordering reported by Allison et al.¹³¹

Table 1.4: Percentage of Schizophrenia Patients Experiencing a ≥ 7 Percent Increase in Body Weight from Baseline in Randomized Controlled Trials: A Comparison of Second-Generation Antipsychotic Agents to Placebo³⁵⁻⁴⁰

Antipsychotic	Antipsychotic %	Placebo %	Net Difference %
Aripiprazole ***	8	3	5
Olanzapine *	29	3	26
Quetiapine**	23	6	17
Risperidone *	18	9	9
Ziprasidone **	10	4	6

Trial Duration: * 6-8 week; ** 4-6 week; *** 'Short-term.'

Net Difference: Percentage experiencing a $\geq 7\%$ increase in body weight on antipsychotic therapy minus percentage achieving a $\geq 7\%$ increase in body weight on placebo.

Similar findings have been reported in clinical practice. One retrospective analysis examined the relative weight gain potential of a number of second-generation antipsychotics in schizophrenia patients. Clozapine and olanzapine were associated with the highest weight gain (mean maximal weight gains of $7.5 \pm 6.0\text{Kg}$ and $8.0 \pm 6.0\text{Kg}$, respectively) compared to weight increases of $4.1 \pm 3.4\text{Kg}$ with risperidone, and $3.5 \pm 4.1\text{Kg}$ with haloperidol.¹³² The time course over which weight changes occurred is also distinctive. Weight gain associated with olanzapine and clozapine tends to plateau after 20 weeks treatment compared to ten weeks with risperidone.¹³² Other studies have suggested that weight gain with olanzapine does not plateau until 40 to 52 weeks after commencing treatment, with mean weight gains of 12Kg reported for patients prescribed between 12.5 to 17.5 milligrams olanzapine daily.¹³³ In a European study, weight gain was listed as an adverse effect for 74.5 percent of patients treated with olanzapine, compared to 53.4 and 40.0 percent of patients treated with risperidone and haloperidol, respectively.¹³⁴ Using the definition of a seven percent increase or greater in body weight from baseline as being clinically significant, 45.7 percent of patients treated with olanzapine had clinically relevant increases in weight compared to 30.6 treated with risperidone and 22.4 percent with haloperidol.¹³⁴ Data for quetiapine were not conclusive due to the small sample size and short duration of treatment.¹³⁴ However, mean weight increases of 2 to 5.6Kg have been reported with long-term quetiapine therapy.¹³³ Ziprasidone, in contrast, appears to be weight neutral, with no, or minimal mean weight changes reported over one year of treatment.¹³³ Similarly, aripiprazole appears to be weight neutral, with mean weight changes of -1.4Kg and +1Kg reported after 26 and 52 weeks of therapy, respectively, in randomized, clinical trials.^{35;135}

The pattern of weight gain for antipsychotic agents appears to vary according to patient baseline weight. When stratified according to baseline body mass index (BMI), patients with low BMI ($< 23\text{Kg/m}^2$) and normal BMI ($23\text{-}27\text{Kg/m}^2$) typically have larger increases in weight compared to those patients that are overweight (BMI $> 27\text{Kg/m}^2$) when commencing antipsychotic therapy.^{35;37;40} It has been postulated that antipsychotic efficacy may be correlated with increases in body weight; however, study findings have been inconsistent.¹³³

1.8.1.2 Mechanism of Antipsychotic-Induced Weight Gain

The mechanism by which the second-generation antipsychotics induce weight gain is uncertain, but is thought to relate to an increased caloric intake.¹³⁶ This is possibly mediated through the antagonistic effects of these agents at dopamine, serotonin, histamine and acetylcholine receptors.¹³⁶ The relative weight gain associated with the various second-generation agents does not however correlate very well with their relative affinities for these receptors.¹³⁷ Proposed mechanisms for weight gain include: antagonism of dopamine D_2 and serotonin 5-HT₂ receptors leading to increased feeding; anticholinergic effects causing dry mouth thereby stimulating thirst which may be quenched using high caloric drinks; and antihistaminic H_1 effects leading to sedation and decreased activity.¹³⁷ Additional hypotheses regarding antipsychotic-induced weight gain relate to their effects on tumor necrosis factor-alpha (TNF- α) and leptin.¹³⁶ Increased serum levels of these cytokines have been documented with clozapine and olanzapine treatment.^{136;138} TNF- α affects glucose, protein and lipid metabolism whereas leptin is thought to regulate appetite and weight by acting on leptin receptors in the satiety center in the hypothalamus.^{136;138} Leptin is normally synthesized by adipocytes in response to insulin, with increased leptin levels also noted in response to insulin resistance and hyperinsulinemia.¹³⁸ As the

second-generation antipsychotics have been noted to cause increased serum insulin levels, elevated leptin levels may be secondary to the effect of these agents on insulin secretion, although a direct effect on leptin production cannot be excluded.¹³⁸ Weight gain with these agents may alternatively be due to insulin, which causes weight gain by a direct effect on adipose tissue and also by hypoglycemia-induced increased appetite.¹³⁸

1.8.1.3 Weight Gain Associated with Other Psychotropic Medications

A number of other psychotropic medications have been implicated with regard to weight gain. Weight gain associated with antidepressant therapy is variable and relates to the dose, duration of therapy and agent use.¹³⁹ Lithium and mood stabilizing agents such as valproic acid and carbamazepine have well documented weight gain potential. Lithium-induced weight gain is dose dependent and may be considerable with a mean weight gain of 10Kg over six to ten years reported, with weight gain occurring in one-third to two-thirds of patients.¹³⁹ Similarly, weight gain is common with valproic acid, with up to 59 percent of patients gaining between 8 to 14Kg, and is related to the duration of treatment.¹³⁹ Weight gain is a common cause of patient non-adherence and premature treatment discontinuation.¹³⁹

1.8.1.4 Summary

In summary, weight gain is commonly reported with the second-generation antipsychotic agents. The magnitude of weight gain appears to be greatest with clozapine and olanzapine, with aripiprazole and ziprasidone appearing to be weight neutral. The situation may be further exacerbated for patients requiring concomitant treatment with other psychotropic agents known to cause weight gain. Obesity and weight gain are important issues for patients with serious mental illness. The prevalence of overweight and obesity in patients with schizophrenia and bipolar disorder has been documented to exceed that of

the general population independent of antipsychotic use.¹⁴⁰⁻¹⁴⁴ Aside from the immediate implications for treatment adherence, obesity and weight gain are associated with an increased risk of morbidity and mortality. The benefits of treatment with the various antipsychotic agents must be balanced against their relative potential to cause weight gain.

1.8.2 Glucose Dysregulation

The use of the second-generation antipsychotics has been associated with reports of glucose dysregulation, including new-onset diabetes and cases of acute metabolic decompensation including diabetic ketoacidosis. While double-blind, randomized, placebo-controlled clinical trials may help to establish a causal relationship; these studies are limited in number. Nonetheless, support for causality can be derived from the multitude of published reports. These include: case reports; adverse drug reaction surveillance reports; clinical studies; prevalence studies; case-control studies; and retrospective cohort studies. These reports are examined in detail here and the case for a causal association between use of second-generation antipsychotics and development of hyperglycemia built.

1.8.2.1 Case Reports

In 1994, the first case reports of possible glucose dysregulation secondary to the use of second-generation antipsychotics appeared in the literature.^{145;146} Since then a total of 99 published cases of glucose dysregulation in adults aged 18 years or older, have been identified.¹⁴⁵⁻²⁰⁰ (Appendix A) Clozapine (N=30) and olanzapine (N=59) were most frequently implicated, with fewer reports attributed to risperidone (N=6), quetiapine (N=3)^{163;169;198} and ziprasidone (N=1)¹⁸⁸. In 14 cases, patients were receiving dual antipsychotic therapy, nine of whom were receiving concomitant first-generation antipsychotic therapy. Other combinations used included: clozapine with risperidone (N=1)¹⁴⁹; clozapine with

ziprasidone (N=1)¹⁸⁸; quetiapine with risperidone (N=1);¹⁹⁸ and olanzapine with quetiapine (N=1).¹⁷⁴ One patient was receiving a combination of olanzapine, zotepine (a second-generation antipsychotic licensed in Europe and Asia) and a first-generation antipsychotic.¹⁹⁹ In each case, the authors proposed a single causative agent on the basis that the patient had been maintained without adverse effect on one agent, that glucose dysregulation commenced subsequent to the second agent being added and resolved on its discontinuation. The descriptive data on demographic variables, medications, diagnoses and risk factors for diabetes are presented in Table 1.5.

Table 1.5: Descriptive Analysis of 99 Published Cases of Glucose Dysregulation Associated with Second-Generation Antipsychotic Therapy

Variable	N	% ¹
Second-Generation Antipsychotic		
Clozapine	30 ²	30.3
Olanzapine	59 ³	59.6
Quetiapine	3 ⁴	3.0
Risperidone	6	6.1
Ziprasidone	1 ⁵	1.0
Gender		
Male	74	74.7
Female	25	25.3
Race		
African American	30	30.3
Asian	6	6.1
Black ⁶	5	5.1
Caucasian	37	37.4
Hispanic	1	1.0
Not Reported	20	20.2
Age Group		
18-44	58	58.6
45-64	36	36.4
65-74	2	2.0
≥75	1	1.0
Not Reported	2	2.0
Baseline Body Mass Index Category Kg/m²		
Normal (18.5-24.9)	8	8.1
Overweight (25-29.9)	27	27.3
Obese Class I (30-34.9)	18	18.2
Obese Class II (35-39.9)	8	8.1
Obese Class III (≥ 40)	2	2.0
Not Reported	36	36.4
Family History of Diabetes		
Yes	28	28.3
No	43	43.4
Not Reported	28	28.3
Mental Disorder Diagnosis		
Schizophrenia	55	55.6
Schizoaffective Disorder	17	17.2
Bipolar Disorder	8	8.2
Psychotic Disorder	4	4.0
Depressive Disorder	8	8.1
Not Reported	7	7.1

Table 1.5: Descriptive Analysis of 99 Published Cases of Glucose Dysregulation Associated with Second-Generation Antipsychotic Therapy (continued)

Variable	N	% ¹
Event		
New-Onset Diabetes Mellitus	55	55.6
Diabetic Ketoacidosis	27	27.3
Decreased Glycemic Control	10	10.1
Hyperosmolar, Hyperglycemic, Nonketonic Coma	3	3.0
Transient Hyperglycemia	3	3.0
Diabetic Coma	1	1.0
Time to Event (weeks)		
1-4	25	25.3
5-9	14	14.1
10-12	14	14.1
13-26	16	16.2
27-52	12	12.1
>52	14	14.1
Not reported	4	4.0
Maximum Blood Glucose Level Reported (mg/dL)		
<300	22	22.2
300-499	27	27.3
500-999	31	31.3
≥ 1000	13	13.1
Not Reported	6	6.1
Percentage Hemoglobin A_{1C} (HbA_{1C}) Level at Time of Event		
6.0-7.0	3	3.0
7.1-8.0	0	0.0
8.1-12.0	8	8.1
12.1-14.0	7	7.1
≥ 14.1	4	4.0
Not Reported	77	77.8
Treatment Associated Weight Gain		
No Weight Gain	8	8.1
< 6.7 Kg	15	15.2
6.8 – 13.6 Kg	18	18.2
≥ 13.7 Kg	12	12.1
Weight Gain -amount not specified	5	5.1
Weight Loss	11	11.1
Not Reported	30	30.3

1. Figures may not sum to 100%, due to rounding.
2. One patient on dual therapy with risperidone; clozapine presumed to be the causative agent.
3. Dual therapy (N=1 quetiapine; N=1 ziprasidone); olanzapine presumed to be the causative agent.
4. One patient on dual therapy with risperidone; quetiapine presumed to be the causative agent.
5. Patient on dual therapy with clozapine; ziprasidone presumed to be the causative agent.
6. Black race includes: African; Afro-Caribbean and Aboriginal.

The majority of cases were men (N=74), with African Americans (N=30) and Caucasians (N=37) most frequently affected. Patients ranged in age from 18 to 79 years, with a mean age of 41.8 years (SD: 10.7). Among the 69 patients for whom weight changes were reported, treatment associated weight gain was documented in 50 patients, of whom 30 gained in excess of 6.8Kg (15 pounds), and 12 gained in excess of 13.7Kg (30 pounds). Data on body mass index available for 62 patients indicated that 89 percent of patients were overweight (N=27) or obese (N=28) at baseline. Twenty-nine patients (29.3%) had a positive family history for diabetes. Three patients had a history of impaired glucose tolerance. A mental disorder diagnosis was provided for 92 patients, of whom the majority (78%) was being treated for schizophrenia or schizoaffective disorder. Mean daily doses of the antipsychotics used were: clozapine 399.0 milligrams (SD: 248.7mg); olanzapine 16.9 milligrams (SD: 7.4mg); and risperidone 7.0 milligrams (SD: 3.0mg).

Eighty-six patients (86%) were diagnosed with new-onset diabetes. The time to onset of diabetes ranged from 4 days to 5 years, with over 50 percent of cases occurring within three months, and over two-thirds of cases (69.7%) occurring within six months of initiating therapy. Of note, 27 of these patients presented directly as diabetic ketoacidosis (DKA) (31%), with one patient presenting with a diabetic coma,¹⁷¹ and three with hyperglycemic, hyperosmolar nonketonic coma.^{180;192;200} At the time of diagnosis, 76 percent of patients had a blood glucose level greater than 300mg/dL, and 48 percent a value greater than 500mg/dL. Baseline hemoglobin A_{1C} (HbA_{1C}) levels were infrequently reported (N=21) but ranged from 6.1 to 18.6 (mean 12.2, SD: 3.4) in patients without a previous diagnosis of diabetes. Ten patients with preexisting diabetes experienced loss of glycemic control beginning between four days and 18 weeks subsequent to commencing antipsychotic therapy.^{149;162;179;184;190;200}

In 50 percent of patients, the hyperglycemia resolved with either discontinuation of antipsychotic therapy (N=31); switching to an alternative antipsychotic (N=8); dose reduction (N=1); using dietary control (N=2) or resolved spontaneously despite continuing antipsychotic therapy (N=5). Five patients experienced a recurrence of hyperglycemia when rechallenged with therapy.^{149;154;155;161;191} Forty-one patients maintained on antipsychotic therapy (either first or second-generation) required ongoing therapy for their diabetes (insulin N=17; oral hypoglycemic therapy N=24). Five patients experienced ongoing diabetes mellitus, and one impaired glucose tolerance, despite discontinuation of all antipsychotic therapy.^{148;149;153;171;184;199} Three patients died.^{150;185;192}

In order to identify risk factors that may predispose a patient to the development of DKA, a comparison of patients who presented with new onset diabetes alone compared to those who presented with DKA was conducted. No significant differences were found between the two cohorts based on gender, race, being overweight at baseline, having a family history of diabetes, the duration of antipsychotic therapy or the HbA_{1C} levels at presentation. (Table 1.6)

Table 1.6: Comparison of Patient Characteristics for Patients Treated with Second-Generation Antipsychotic Agents Developing New Onset Diabetes Mellitus (DM) Only or Diabetic Ketoacidosis (DKA)

Variables	DM only (N=55) %	DKA (N=27) %	t test or χ^2	p
Gender (male)	76.4	77.8	0.02	0.887
Race (African American)	32.7	48.1	1.83	0.228
Overweight at baseline (N=53)	91.7	94.1	0.10	0.753
Treatment associated weight gain (N=56)	72.5	68.8	0.08	0.779
Family history of diabetes	32.7	29.6	0.08	0.777
Mean (SD)				
Age (years) (N=80)	42.2 (10.1)	37.1 (8.5)	2.24	0.028
Duration of treatment (weeks) (N=78)	31.1 (45.3)	24.5 (28.8)	0.68	0.496
Maximum blood glucose (mg/dL) (N=75)	441 (253)	789 (297)	5.50	<0.001
HbA _{1C} at time of event (%) (N=19)	12.2 (3.4)	12.7 (3.3)	0.37	0.711
Clozapine dose (mg) (N=22)	462 (325)	325 (118)	1.55	0.142
Olanzapine dose (mg) (N=44)	16.4 (7.7)	17.7 (7.5)	0.52	0.604
Baseline BMI (Kg/m ²) (N=34)	29.6 (5.0)	30.6 (5.6)	0.571	0.572
Treatment associated weight gain (Kg) (N=39)	11.4 (7.9)	12.0 (9.7)	0.195	0.874

Patients who developed DKA were found to be younger (mean age difference 5.1 years; $t=2.34$, $df=78$, $p=0.0218$) and as expected, had higher maximum blood glucose levels reported (mean difference 351mg/dL; $t=5.50$; $df=74$; $p<0.001$). When the dose of the two most frequently implicated agents, clozapine and olanzapine was examined, no difference in mean daily dose was found for patients who developed diabetes only, compared to those presenting with DKA.

The markedly different frequency of glucose dysregulation reported for the various second-generation antipsychotic agents cannot entirely be explained by length of time on the market, or number of prescriptions. Based on published case reports, it appears that there is an increased risk of glucose dysregulation for patients treated with clozapine or olanzapine compared to risperidone. The limited use of quetiapine and ziprasidone during the time frame of these reports (1994 to 2004) does not permit comparisons to be made. When compared to a

national prevalence of approximately 12 percent, African American patients appear to be over-represented in this dataset with a prevalence of 30.3 percent. This may reflect a genetic predisposition of this population to diabetes as, of note, national figures from 2002 suggest that among diagnosed diabetics, non-Hispanic blacks were 1.6 times as likely as non-Hispanic whites of a similar age to have diabetes.²⁰¹ At the time of diagnosis, 58.6 percent of patients were aged less than 45 years, a trend which is not consistent with national figures for patients presenting with diabetes.²⁰² Glucose dysregulation occurred in both the presence and absence of weight gain. Nearly 90 percent of patients were overweight or obese prior to commencing treatment with a second-generation antipsychotic however, suggesting that this may be a potential risk factor for the development of glucose dysregulation in these patients. Confusing the issue somewhat is the knowledge that in over 50 percent of patients, glucose dysregulation resolved quite rapidly on discontinuation or switching of antipsychotic therapy and without necessarily being accompanied by any weight loss.

HbA_{1C}, or glycated hemoglobin, is used as a measure of average glycemic control over a 120 day period, with each one percent increase in HbA_{1C} correlated with a 35mg/dL increase in mean plasma glucose.²⁰³ HbA_{1C} levels were rarely measured in these patients; however, a mean baseline HbA_{1C} of 12.2 (SD: 3.4) correlates with a mean plasma glucose level of 352 mg/dL (SD: 119) in the preceding 120 days. For patients newly diagnosed with diabetes soon after commencing an antipsychotic, a high HbA_{1C} at the time of diagnosis may imply that the diabetes pre-dated the use of the antipsychotic. This possibly oversimplifies the relationship between HbA_{1C} and mean plasma glucose, however, as the HbA_{1C} may be viewed as a “weighted” average of plasma glucose levels.²⁰³ That is, HbA_{1C} levels are influenced most by the plasma glucose levels

in the proximate weeks, and can increase rapidly with large changes in plasma glucose.²⁰³

Of major concern is the fact that 31 percent of patients presented with hyperglycemic crisis (DKA, diabetic coma or hyperosmolar hyperglycemic coma). These life-threatening conditions are typically rare in patients with type 2 diabetes and usually manifest only secondary to a stressor such as an infection.²⁰⁴ With the exception of younger age, no predictors for the development of DKA were found. The preponderance of these cases in this series may reflect a publication bias toward serious or unusual cases. Alternatively, it may reflect the mechanism by which the second-generation antipsychotics induce glucose dysregulation, that is, by both induction of peripheral insulin resistance and the impairment of insulin secretion.

While acknowledging that neither incidence nor prevalence can be determined from case reports, there appears to be an association between the use of second-generation antipsychotics and the development of new-onset diabetes. The findings of this review of published case reports is consistent with an earlier report by Jin et al.²⁰⁵ It is unclear from these case reports if the difference in report frequency for the five second-generation antipsychotic agents reflects differences in their prescribing frequency, or differences in their effect on glucose regulation or adiposity or both, or merely a reporting bias.

1.8.2.2 Case Series and Adverse Event Reports

As noted, case reports are particularly susceptible to bias as they involve a small and highly selective group of patients. To strengthen the case for a causal relationship between the use of second-generation antipsychotics and the development of glucose dysregulation, case series and adverse event reports may be examined. While acknowledging limitations associated with these reports (such as the absence of a comparator group, their retrospective nature and the

fact that they represent a survival cohort) these reports involve larger numbers of patients than case reports and are thereby a useful tool in demarcating the clinical problem.²⁰⁶

Using the Ohio Department of Mental Health database to identify patients treated in a state hospital, Wilson et al. conducted a retrospective review of patients who were treated with a second-generation antipsychotic and who were also evaluated or treated for diabetes mellitus.²⁰⁷ Of a total of 126 patients treated, 14 patients had blood glucose levels performed or were evaluated for glucose intolerance or diabetes.²⁰⁷ New-onset diabetes was documented in 11 patients following treatment initiation with clozapine, olanzapine, or quetiapine, or addition of risperidone to clozapine.²⁰⁷ Five of these patients developed diabetic ketoacidosis, with a median time to onset of 33 days.²⁰⁷

In a series of reports by Koller et al. summarizing the submissions to the voluntary adverse drug reporting scheme (MedWatch), the association between the use of clozapine, olanzapine, quetiapine and risperidone and the development of hyperglycemia was examined.⁵⁻⁸ A total of 798 cases (clozapine (N=384); olanzapine (N=237); quetiapine (N=46); risperidone (N=131)) of new-onset hyperglycemia were identified.⁵⁻⁸ These included new-onset diabetes (clozapine (N=242); olanzapine (N=188); quetiapine (N=34); and risperidone (N=78)); exacerbations of existing diabetes (clozapine (N=54); olanzapine (N=44); quetiapine (N=8); risperidone (N=46)); and cases of diabetic ketoacidosis (clozapine (N=80); olanzapine (N=80); quetiapine (N=21); risperidone (N=26)).⁵⁻⁸ A total of 55 fatalities were reported (clozapine (N=25); olanzapine (N=15); quetiapine (N=11); risperidone (N=4)).⁵⁻⁸ The majority of cases were reported within six months of initiating therapy with the antipsychotic agent (range 60 to 75%), with approximately 23 percent of cases occurring within one month of initiating therapy (range 17 to 31%).⁵⁻⁸ The mean age at presentation was similar

for all four drugs (clozapine: 40.0 ± 12.0 ; olanzapine: 39.8 ± 12.4 ; quetiapine: 35.3 ± 16.2 ; and risperidone 39.8 ± 17.4) with patients presenting with new-onset cases consistently younger than those experiencing exacerbation of preexisting-diabetes.⁵⁻⁸ The majority of cases were men (male: female ratio range: 1.5-2.0).⁵⁻⁸ No association between time to onset, or severity of hyperglycemia and dose of antipsychotic used was established.⁵⁻⁸ The authors suggest a causal relationship between the use of these agents and the development of hyperglycemia due to: the number of reports; the temporal relationship to treatment initiation; and the prompt reversal of hyperglycemia on antipsychotic discontinuation. In addition, patients were typically younger than anticipated by national data for patients presenting with type 2 diabetes, with a disproportionate number of male cases compared to national data.⁵⁻⁸ It is unclear if the disparity in the number of cases reported represents a reporting bias, differences in drug utilization rates, or a genuine difference in risk between the individual drugs. However, while relatively fewer cases of hyperglycemia were reported for risperidone, the number of cases for this agent were considerably higher than for the first-generation antipsychotic, haloperidol (reporting ratio 8.5:1 based on prescription sales data).⁶ Furthermore, for quetiapine, an agent approved by the FDA in September 1997, an increase in the number of hyperglycemic events reported was documented with increasing patient exposure as measured by the number of prescriptions dispensed each year.⁷

Similar findings to that of Koller et al. were documented in a study using the World Health Organization database for adverse drug reactions.²⁰⁸ In it a significant association between the use of clozapine, olanzapine and risperidone and the development of glucose intolerance was documented.²⁰⁸ Furthermore, potential risk factors for glucose intolerance in patients taking second-generation antipsychotics were identified. Specifically, male gender; an increase in weight;

concomitant use of valproic acid, selective serotonin reuptake inhibitors or buspirone; or an underlying diabetic condition were significantly associated with the development of glucose intolerance.²⁰⁸

As noted previously, while neither causality nor relative risk can be established using case series or adverse event reporting, these reports serve to support the hypothesis that the use of second-generation antipsychotics may precipitate hyperglycemia, the onset of which may be rapid and severe.

1.8.2.3 Retrospective Clinical Studies

To further the hypothesis of a causal relationship between use of the second-generation antipsychotics and the development of glucose dysregulation, retrospective clinical studies which support the biological plausibility of the hypothesis will be presented. Kinon et al. conducted a retrospective chart review comparing patients treated with olanzapine (N=573) and haloperidol (N=103) for up to three years. Patients treated with olanzapine had significantly higher mean weight gains (6.26Kg vs. 0.69Kg, $p < .001$) and a higher median nonfasting serum glucose level (99.1mg/dL vs. 93.7mg/dL, $p=0.01$).²⁰⁹ In a similar study published by Meyer et al. comparing the metabolic outcomes during the first year of therapy for patients treated with either olanzapine (N=47) or risperidone (N=47), no significant difference was found between the groups in terms of serum glucose or weight gained.²¹⁰ After stratifying the patients according to age, olanzapine was associated with significantly greater increases in plasma glucose than risperidone (+10.8mg/dL vs. 0.74mg/dL, $p=0.03$) but a non-significant difference in weight gain (+20.4lb vs. +11.9lb, $p=0.091$) in patients aged less than 60 years.²¹⁰

Wirshing et al. documented changes in mean plasma glucose levels in 215 patients treated with antipsychotic therapy (clozapine (N=39); olanzapine (N=32); risperidone (N=49); quetiapine (N=13); haloperidol: (N=41) and

fluphenazine (N=41)).²¹¹ Increases in mean plasma glucose levels from baseline were noted for all six agents ranging from a three percent increase for risperidone (+4mg/dL) to a 21 percent increase with olanzapine (+22.2mg/dL).²¹¹ Increases for clozapine, olanzapine and haloperidol were significant at the 0.05 level.²¹¹ New-onset diabetes requiring initiation of a glucose lowering agent was required in five patients (13%) treated with clozapine. Two patients with a past history of diabetes and stabilized on a glucose-lowering agent required an increased dose to control their glucose level following initiation of olanzapine.²¹¹

The impact of clozapine on serum insulin levels was examined in a small study which compared patients treated with clozapine (N=13) to those treated with first-generation antipsychotics (N=28).²¹² The clozapine patients had higher insulin levels, lower median insulin-like growth factor I (IGF-I) levels, but similar BMI and fasting blood glucose levels to patients treated with the first-generation antipsychotics.²¹² Serum insulin levels were found to be positively correlated with serum clozapine concentrations, but were not correlated to serum concentrations of the first-generation antipsychotics. The authors hypothesized that clozapine induces peripheral insulin resistance and a secondary increase in insulin secretion. Consistent with this, Henderson et al. reported significant insulin resistance and impairment of glucose effectiveness with clozapine and olanzapine, compared to risperidone in a cross-sectional study of stable, non-obese schizophrenia patients using a frequently sampled intravenous glucose tolerance test.²¹³ Likewise, Newcomer et al. documented significantly abnormal glucose tolerance tests in patients treated with clozapine and olanzapine, but not risperidone or first-generation antipsychotics.²¹⁴

A number of these studies were limited by small sample sizes, absence of control groups, and an inability to confirm fasting blood glucose levels. Reports conflicted regarding the proposed mechanism by which the second-generation

antipsychotics induce glucose dysregulation, specifically regarding the development of insulin resistance. Regardless of the mechanism by which the second-generation antipsychotic agents induce glucose dysregulation, these studies all support the theory that the second-generation antipsychotics, and specifically clozapine and olanzapine, induce hyperglycemia and glucose dysregulation which may be independent of weight gain or BMI.

1.8.2.4 Prevalence Studies

Cross-sectional or prevalence studies provide somewhat more robust support of the hypothesis of second-generation antipsychotic induced-glucose dysregulation than the information heretofore presented. These studies minimize the risk of selection bias, but are still susceptible to the effects of confounding and measurement bias.²¹⁵ Nonetheless, they help to corroborate the hypothesis and are, therefore, included here.

A number of cohort studies have examined the prevalence of diabetes among patients taking second-generation antipsychotics.²¹⁶⁻²²³ The prevalence of diabetes and impaired glucose tolerance in these studies ranged from nine to 36.6 percent, and in each instance was significantly greater than that noted in a similar age-matched general population. Association between the prevalence of glucose dysregulation and the class of antipsychotic (first or second-generation), or specific second-generation agent used varied. The results of a number of these studies will now be highlighted.

In a prospective study, Hagg et al. assessed the prevalence of diabetes mellitus or impaired glucose tolerance in patients treated with clozapine (N=63) compared to patients treated with depot preparations of first-generation antipsychotics (N=67).²¹⁶ Diabetes mellitus or impaired glucose tolerance was documented in 22 percent of clozapine patients compared to 10 percent of the control group, although the difference was not statistically significant

($p=0.06$).²¹⁶ Henderson et al. published a five-year naturalistic study in which 30 new cases of diabetes were diagnosed among 82 non-diabetic patients (36.6%) treated with clozapine.²²³ The development of diabetes was not found to be associated with changes in weight (despite documentation of a significant increase in weight equating to 0.5 Kg / month ($p < 0.001$)), use of valproate or total daily dose of clozapine.²²³ In a similar study, Gupta et al. noted a prevalence of diabetes of 17 percent in a cohort of 208 patients (mean age 46 years (SD 14.5)) with serious mental illness receiving monotherapy with either a first or second-generation antipsychotic.²²¹ No difference in the prevalence of diabetes was found between the different antipsychotic agents.²²¹

Using data from the Veterans Health Administration of the Department of Veterans Affairs (VA), Sernyak et al. conducted a retrospective review comparing the prevalence of diabetes in 38,632 outpatients with schizophrenia receiving treatment with first- and second-generation antipsychotics.²²² The prevalence of diabetes did not differ between patients receiving treatment with first- and second-generation antipsychotics with rates of 18.64 percent and 18.84 percent, respectively.²²² After controlling for the effect of age, patients receiving second-generation agents were noted to be significantly more likely to have diabetes (odds ratio (OR): 1.09; 95% CI: 1.03-1.15, $p=0.002$) compared to those receiving a first-generation antipsychotic.²²² Stratifying by age, the effect was most pronounced for those aged less than 40 years (OR: 1.63; 95% CI: 1.23-2.16, $p=0.001$) with prevalence rates of 6.2 to 8.7 percent noted.²²² In contrast to the study by Gupta et al., a significant difference in the prevalence of diabetes was found between the different antipsychotic agents.^{221;223} Specifically, there was a significant association between the use of clozapine, olanzapine and quetiapine, but not risperidone, and a diagnosis of diabetes.²²²

Clearly prevalence data cannot be used to determine the incidence of diabetes associated with the use of second-generation antipsychotics. These data merely serve to highlight the high prevalence of diabetes among patients with serious mental illness prescribed antipsychotic agents. The prevalence of diagnosed diabetes in these studies exceeds that of the general U.S. population at approximately 5.4 percent in 2002.²²⁴ This may relate to the use of antipsychotics, to a more diabetogenic lifestyle, or a genetic predisposition of this vulnerable population to the development of diabetes. In any case, the trend is worrying given the increased morbidity and mortality associated with diabetes.²⁰⁴

1.8.2.5 Case-Control and Cohort Studies

Recent cohort studies have also supported the evidence for a causal relationship between the use of second-generation antipsychotics and the development of diabetes, by comparing incidence rates in patients exposed to second-generation antipsychotics to those exposed either to no therapy, or to first-generation antipsychotic agents. These studies will now be reviewed in detail.

1.8.2.5.1 General Findings

A total of five case-control^{3;10;225-227} and 27 retrospective cohort studies that used large claims^{4;9;228-250} or clinical trials databases^{251;252} were identified. (Appendix B) The majority of the studies were conducted using claims data from the U.S., with three studies using claims data from Canada;^{230;232;245} four using data from the United Kingdom (U.K.);^{3;4;10;229} and one using Italian-based data.²⁴⁸ Among the U.S. studies, four databases incorporated Medicaid data;^{226;227;239;243} four examined Veterans Affairs databases;^{228;231;235;242} eleven used databases from private health care plans;^{9;234;236-238;240;241;244;246;247;250} three used data from hospital inpatients or ambulatory care clinics;^{225;233;249} and two conducted post-hoc analyses of data from clinical trials databases.^{251;252} These

studies varied according to the inclusion criteria, that is, inclusion of schizophrenia patients only (N=7);^{3;226;231;242;246;250;251}, patients with schizophrenia or a mood disorder only (N=2);^{239;240} any patient with psychosis (N=2);^{236;237} patients with mood disorders (N=1);²³⁸ patients with dementia (N=1);²⁵² patients with a mental health diagnosis (N=2);^{227;244} and those studies that included all patients treated with an antipsychotic agent (N=16).^{4;9;10;225;228-230;232-235;241;245;247-249} Studies also varied according to how they classified incident diabetes. Classifications included: an International Classification of Diseases, 9th Revision (ICD-9) code of 250.xx; a prescription for a diabetic medication (oral hypoglycemic agent or insulin); a blood glucose level of 200mg/dL or greater; a glycated hemoglobin (HbA_{1c}) greater than nine percent; or a combination thereof. Studies also varied according to the level of pre-screening for diabetes in determining incident cases, and if they limited, or did not limit enrollees to antipsychotic monotherapy. Exclusion periods ranged from zero to twelve months prior to study enrollment.

When compared to untreated patients, variable relative risks (RR) of developing diabetes were documented, that is, clozapine (N=5, RR: 0.78-7.44*);^{9;227;234;236;239} olanzapine (N=9, RR: 1.00–5.8*);^{3;9;229;234;236-240} risperidone (N=9, RR: 0.66-3.7*);^{3;9;229;234;236-240} quetiapine (N=5, RR: 0.98-1.9*);^{9;234;237;239;240} a first-generation antipsychotic (N=12, RR: 0.885-4.97);^{3;4;9;10;229;232;234;236-240} and any second-generation antipsychotic agent (N=7, RR: 0.9-4.7*);^{4;9;10;229;232;234;239} Sacchetti et al. also used an untreated population as the comparator group, however, the hazard ratios reported were highly inflated by comparison, most likely because of the small sample sizes.²⁴⁸ When compared to patients treated with first-generation antipsychotic agents, the relative risk of developing diabetes again varied according to the study, that is, clozapine (N=8, RR: 1.2-2.1*);^{9;226;231;234;242-244;253} olanzapine (N=10, RR: 0.9–4.2*);

* Statistically significant finding

^{3;9;225;226;231;233;234;241;242;250} quetiapine (N=7, RR: 0.7*-3.3*),^{9;225;226;231;234;242;244} risperidone (N=10, RR: 0.7*-4.1*),^{3;9;225;226;231;233;234;241;242;250} and any second-generation agent (N=9, RR: 0.9-2.6*).^{3;4;228;229;234;241;246;247;250}

A number of studies also directly compared the relative propensities of the second-generation antipsychotics to induce diabetes. When compared to risperidone, patients treated with olanzapine were documented to have an increased risk of diabetes in seven studies (RR: 1.2*-4.2*);^{229;230;235;236;238;245;247} and a reduced or comparable risk in five studies (RR: 0.3*-1.0).^{9;232;241;248;250} Patients treated with clozapine were documented to have an increased risk of diabetes relative to those treated with risperidone (N=2; RR: 1.1-8.4*),^{236;247} as were those treated with ziprasidone (N=1; RR: 2.64).²⁴⁷ In contrast, those treated with quetiapine were found to have a comparable or lower risk (N=3; RR: 0.7-1.0)^{232;247;248} of diabetes. Relative to olanzapine, no statistical difference in risk of diabetes was reported with clozapine (N=2; RR: 0.8-1.5), quetiapine (N=2; RR: 1.2 (N=1 reported as ‘non-significant’)) or risperidone (N=3; RR: 0.8-1.0).^{246;248;249} Many of these studies documented statistically significant findings; however, it is worth remembering that a relative risk of two or greater is generally recommended when reporting clinical significance. Of interest, of the five studies sponsored by Eli Lilly and Co., the manufacturers of Zyprexa® (olanzapine), three reported a favorable risk for olanzapine compared to risperidone, with two studies reporting an increased, albeit non-statistical difference in risk.^{9;229;241;247;250} Four of the five studies favoring risperidone over olanzapine were sponsored and co-authored by Janssen Pharmaceutica, the manufacturers of Risperdal® (risperidone),^{230;235;236;245} with the fifth study sponsored by AstraZeneca Pharmaceuticals, the manufacturers of Seroquel® (quetiapine).²⁴⁵ Studies reporting comparable risk between the two agents did not report sponsorship or were independently sponsored.^{232;246;248;249}

1.8.2.5.2 Antipsychotic Dose and Diabetes Risk

The possibility that the association between antipsychotic use and the development of diabetes is a dose-related effect is an important issue. This association was examined in seven studies.^{9;226;227;236;238-240} No relationship was noted in a study by Wang et al. that compared patients with a mental health diagnosis treated with clozapine to those not on antipsychotic treatment.²²⁷ Patients were stratified into four quartiles based on the distribution of mean daily dose of clozapine (17-225mg; 226-452mg; 453-572mg; 573-1618mg). Daily doses of 300 to 900 milligrams clozapine have been documented to be effective in patients with schizophrenia with the mean and median dose reported to be 600 milligrams daily.³⁶ Using this dose, more than 75 percent of patients received low doses of clozapine, possibly due to the older age of patients in the study (mean age 61.9-63.6 years).²²⁷ This may have limited the power to detect a dose-response relationship. In addition, there were a limited number of control patients relative to cases in this study, thereby limiting the power to detect an effect should one have existed.

A possible dose-response with quetiapine, but not olanzapine or risperidone, was documented in a study by Buse et al. This study did not limit enrollment to patients with a specific mental health diagnosis, rather it included any patient treated with antipsychotic therapy. The mean daily doses of antipsychotic reported were low, for example: olanzapine 5.1 milligrams (SD: 4.2mg); quetiapine 79.9 milligrams (SD: 96.7mg); and risperidone 1.2 milligrams (SD: 1mg); a limitation acknowledged by the authors, but refuted by them because of the wide range of doses used.⁹

Lambert et al. reported a possible dose-response with olanzapine in a case-control study of schizophrenia patients enrolled in California Medicaid. Patients in this study were stratified as receiving low, medium or high dose

second-generation antipsychotic therapy based on the empirical distribution of the actual doses and expert clinical knowledge. By this system, 20 percent of patients received low-dose therapy (clozapine <300mg; olanzapine < 7.5mg; quetiapine <250mg; risperidone <3mg), 43.2 percent received medium-dose therapy (clozapine 300-600mg; olanzapine 7.5-12.5mg; quetiapine 250-500mg; risperidone 3-6mg) and 36.8 percent high-dose therapy (clozapine >600mg; olanzapine > 12.5mg; quetiapine >500mg; risperidone >6mg). Using any dose of a first-generation antipsychotic as a comparator, no association between antipsychotic dose and risk of diabetes was noted for any agent using 12 or 24-week exposure windows. Using a 52-week exposure window, a possible dose-response was seen for olanzapine where the odds ratio for low-dose therapy (OR=1.25; 95% CI: 1.00-1.57) was significantly smaller than for medium (OR=1.84; 95% CI: 1.53-2.22) or high doses (OR=1.87; 95% CI: 1.58-2.21).²²⁶

Gianfrancesco et al. have published widely in this area. In a study published in 2002 involving psychosis patients enrolled in a private managed health care plan, a possible dose-response was seen for patients treated with olanzapine, but not clozapine or risperidone. Compared to untreated patients, the odds of diabetes increased significantly (OR: 1.22, $p<0.002$) for each 2.6 milligram increase in olanzapine dose.²³⁶ Similarly, in a study published in 2003 of patients with mood disorders enrolled in private managed care plans, a significant dose-response was noted for olanzapine (2.6mg dose-increment OR: 1.34, $p<0.0001$), but not risperidone or first-generation antipsychotics.²³⁸ The mean daily dose of olanzapine used in these studies were 9.4 milligrams (SD: 5.2mg) and 8.9 milligrams (SD: 4.7mg), respectively.^{236;238} Mean daily risperidone doses were 2.3 milligrams (SD: 1.8) and 2.1 milligrams (SD: 1.7mg), respectively.^{236;238} In a study published in 2006 involving Ohio Medicaid enrollees with a diagnosis of schizophrenia, bipolar disorder or major depressive

disorder, the authors reported a ten to 25 percent increase in risk of diabetes with medium or high-dose therapy compared to low-dose or no antipsychotic treatment.²³⁹ Also published in 2006 by the same authors was a study examining antipsychotic-related diabetes in patients with schizophrenia, bipolar disorder or major depressive disorder enrolled in a managed care plan. The authors noted that the odds of new-onset diabetes generally increased with increasing dose of the second-generation antipsychotics. Compared to untreated patients, the odds of developing diabetes was significantly increased for patients receiving high dose risperidone, medium or high dose olanzapine, and any dose of a first-generation antipsychotic.²⁴⁰

In summary, there are conflicting reports of an association between antipsychotic dose and the emergence of new-onset diabetes. A possible relationship has been reported for clozapine, olanzapine, and quetiapine with medium or high-dose therapy compared to no, or low-dose antipsychotic therapy. The discrepancies between the results may result from differences in dose calculations and stratifications, as well as differences in treatment duration, indication and dose, and the comparator chosen.

1.8.2.5.3 Treatment Indication and Diabetes Risk

Treatment indication is an important consideration in any study examining the relationship between antipsychotic use and new-onset diabetes. As will be discussed in detail in section 1.9.7.4, a diagnosis of schizophrenia and affective disorders may predispose patients to diabetes. Failure to control for treatment indication could, therefore, confound the study findings.

The published studies in this area have varied in their inclusion criteria, that is, inclusion of schizophrenia patients only (N=7);^{3;226;231;242;246;250;251}, patients with schizophrenia or a mood disorder only (N=1);²³⁹ any patient with psychosis (N=3);^{236;237;240} patients with mood disorders (N=1);²³⁸ patients with

dementia (N=1); ²⁵² patients with a mental health diagnosis (N=2);^{227;244} and those studies that included all patients treated with an antipsychotic agent (N=16).^{4;9;10;225;228-230;232-235;241;245;247-249} A number of studies (N=16) have attempted to control for differences in treatment indication by including the type of mental health diagnosis (either primary diagnosis or comorbid diagnosis) as a covariate in the logistic regression analyses.

The majority of studies reported a non-significant relationship between diagnosis and occurrence of new-onset diabetes.^{10;228;230;233;236;238-240;242;246;250} Miller et al. reported that mental health diagnoses associated with an increased risk of diabetes were schizophrenia (HR: 1.622, 95% CI: 1.233-2.132), bipolar disorder (HR: 1.355; 95%CI: 1.073-1.711), and post-traumatic stress disorder (HR: 1.691; 95%CI: 1.019-2.806) whereas ‘other psychosis’ was associated with a decreased risk (HR: 0.602; 95%CI: 0.389-0.931) of diabetes. In contrast, in a model comparing patients treated with a first or second-generation antipsychotic, Lee et al. noted a decreased risk of diabetes for patients with bipolar disorder (p=0.425).²⁴¹ Gianfrancesco et al. noted a significant decrease in risk of new-onset diabetes associated with a diagnosis of bipolar disorder (OR: 0.444, p=0.0100) or major depression (OR: 0.449, p=0.0015), but not schizophrenia (OR: 0.445, p=0.1076) compared to other psychoses.²³⁷ In direct contrast, Gianfrancesco et al. reported in a later publication that a diagnosis of schizophrenia significantly increased the risk of new-onset diabetes. When compared to patients with major depression and bipolar disorder, patients with schizophrenia had an increased risk of new-onset diabetes of 40 to 100 percent and 30 to 70 percent, respectively.²⁴⁰

Discrepancies in study findings may relate to differences in the demographics of the different study populations and also to differences in the dose of antipsychotic used for the different treatment indications. As will be

discussed in detail in section 1.10.3, antipsychotic doses used in clinical practice vary according to the indication, age and ethnicity of the population. Failure to control for these variables may confound a possible relationship between antipsychotic use and risk of new-onset diabetes.

1.8.2.5.4 Summary

The conflicting results reported from these case-control and cohort studies may be a result of differences in the classification of incident or new-onset diabetes used, the definition of exposure to an antipsychotic, the number and type of covariates used, together with differences in study duration and study population. The majority of reports appear to indicate an increase in the risk of developing diabetes in patients treated with second-generation antipsychotic agents compared to those treated with first-generation antipsychotics, and to those receiving no treatment. There appears to be an increased risk associated with the use of clozapine and olanzapine relative to risperidone. There is limited data on the use of quetiapine and ziprasidone, with the result that most studies are not adequately powered to detect an effect, should one exist.

1.8.2.6 Prospective Trials

Well-conducted prospective double-blind, randomized controlled-trials with adequate numbers of patients are considered the best-evidence for a cause and effect relationship. The most notable trial in this area is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a randomized active-control trial sponsored by the National Institute of Mental Health (NIMH), published in September 2005. The outcomes from this trial will be discussed in depth. While not necessarily meeting all of the above criteria, the remaining published prospective studies reviewed in this section still serve to provide strong evidence of a causal relationship between use of the second-generation antipsychotics and occurrence of glucose dysregulation.

1.8.2.6.1 The CATIE Study

The CATIE study was a double-blind, active-control clinical trial, conducted between January 2001 and December 2004, and was designed to compare the effectiveness of the first- and second-generation antipsychotic agents. Secondary goals of this study included a comparison of treatment-related adverse effects and specifically, differences in metabolic effects. The trial was limited patients with a diagnosis of schizophrenia aged between 18 and 65 years, who did not have a history of treatment-resistance or serious adverse-effects to the proposed treatment. A total of 1,493 patients were randomized to receive olanzapine (N=330), quetiapine (N=329), risperidone (N=333), ziprasidone (N=183), or the first-generation antipsychotic, perphenazine (N=257) for up to the 18 months.²⁵⁴

The majority of patients were male (74%), white (60%), with a mean age of 40.6 years (SD: 11.1). Prevalent diagnoses at baseline included: diabetes (11%); hyperlipidemia (14%) and hypertension (20%). The mean modal treatment doses were as follows: olanzapine 20.1 milligrams; quetiapine 543.4 milligrams; risperidone 3.9 milligrams; ziprasidone 112.8 milligrams; and perphenazine 20.8 milligrams. Consistent with trends in schizophrenia management, treatment was frequently discontinued with only 26 percent of patients continuing treatment for the planned 18 months. Overall, patients were least likely to discontinue olanzapine (64%) and most likely to discontinue quetiapine (82%) treatment. Similarly the time to treatment discontinuation was longest for olanzapine (median: 9.2 months), compared to quetiapine (4.6 months), risperidone (4.8 months), ziprasidone (3.5 months) and perphenazine (5.6 months). Of note, the agents differed in their rate of discontinuation because of treatment intolerance ($p=0.04$) even after adjusting for duration of exposure.

Olanzapine was the most likely (18%), and risperidone the least likely (10%) to be discontinued owing to intolerability.²⁵⁴

The agents differed significantly regarding treatment-related weight gain and changes in measures of glucose and lipid metabolism. Regardless of treatment duration, olanzapine was associated with the greatest increase in weight ($p<0.001$), glycosylated hemoglobin (HbA_{1c}) ($p<0.001$), cholesterol ($p<0.001$) and triglycerides ($p<0.001$) from baseline and was significantly more likely to be discontinued because of these effects ($p<0.001$) than the other agents. The magnitude of the changes in these parameters is noteworthy. Exposure-adjusted increases in mean blood glucose ranged from 2.9mg/dL (standard error (SE) 3.4) for ziprasidone to 13.7mg/dL (SE: 2.5) for olanzapine ($p=0.59$). Exposure-adjusted changes in glycated hemoglobin (HbA_{1c}) from baseline ranged from 0.04 percent (SE: 0.08) for risperidone to 0.40 percent (SE: 0.07) for olanzapine ($p=0.01$).²⁵⁴ Changes of this scale are only likely to be problematic in a patient with a high baseline risk of diabetes, wherein a relatively small change in blood glucose could shift the patient from pre-diabetes (fasting blood glucose: ≥ 100 mg/dL) to diabetes (fasting blood glucose ≥ 126 mg/dL).

1.8.2.6.2 Glucose Control and Insulin Resistance

Several prospective trials have examined the association between use of second-generation antipsychotics and disruptions in glucose-insulin homeostasis. These open-label studies and short-term randomized controlled trials will now be briefly reviewed.

In a placebo-controlled, open-label study examining olanzapine-induced glucose dysregulation, patients treated with olanzapine experienced significant increases in fasting insulin concentrations and a rapid and significant increase in insulin-resistance. This was not associated with a change in beta cell function; thereby refuting the hypothesis that olanzapine acts as a direct toxin on beta cells

and suggesting instead that the mechanism of glucose dysregulation is due to an induction of peripheral insulin resistance. Compared to controls, patients treated with olanzapine (medication period 8.1 weeks) experienced significant increases in fasting plasma glucose levels (0.7mmol/L versus 0 mmol/L; $p=0.009$), weight (3.3Kg versus 0.6Kg; $p=0.005$) and as noted, fasting insulin concentrations (4.5 μ U/mL versus -1.0 μ U/mL; $p=0.008$) from baseline. While the association between weight gain and insulin resistance is well documented, the authors noted that this is unlikely to be the sole factor contributing to the development of insulin resistance due to the absence of weight gain in some patients and the rapid onset of insulin resistance.²⁵⁵

In a randomized, controlled, double-blind, six-week trial (N=269) comparing olanzapine and ziprasidone, differences in the metabolic profile of the two agents were noted. Compared to ziprasidone, olanzapine was associated with greater increases in weight ($p<0.001$), body mass index ($p<0.0005$), fasting serum insulin ($p=0.051$), C-peptide ($p=0.07$), and homeostasis model assessment insulin resistance logarithm (HOMA-IR[log]) ($p=0.08$) – a measure which takes into account both fasting insulin and fasting glucose measures. Neither agent was noted to significantly affect fasting serum glucose levels with a median increase from baseline of one milligram per deciliter noted for both agents.²⁵⁶

In contrast to the study by Simpson et al.,²⁵⁶ Howes et al. documented significant glucose dysregulation in 11 of 20 schizophrenia patients treated with clozapine that was not associated with significant changes in insulin levels or insulin resistance levels.²⁵⁷ Changes in glucose control were also independent of changes in BMI. The authors hypothesized that glucose dysregulation may be secondary to a direct effect of clozapine in reducing neuronal glucose uptake leading to compensatory increases in glucose levels rather than to clozapine-induced peripheral insulin resistance.²⁵⁷ Moreover, these authors subsequently

found that changes in glucose control do not appear to be related to changes in growth hormone, insulin-like growth factor-1 or insulin-like growth factor binding protein-1 (all important glucoregulatory factors). This supports a theory of a possible direct effect of antipsychotics on central glucose regulation.²⁵⁸

Kingsbury et al. examined the short-term effects of ziprasidone on BMI and serum glucose levels in a six-week, open-label, multi-center study (N=37).²⁵⁹ No significant change in BMI or serum glucose level was documented. Similar findings were documented in a fourteen-week, prospective, randomized trial where clozapine, olanzapine and haloperidol, but not risperidone, were associated with significant increases in plasma glucose levels in 101 patients with schizophrenia or schizoaffective disorder.²⁶⁰

1.8.2.6.2 Summary

While there are some inconsistencies in the findings of the various prospective studies, there nonetheless appears to be a trend towards greater dysregulation of glucose and insulin homeostasis with clozapine and olanzapine than with quetiapine, risperidone and ziprasidone. Given the magnitude of the changes noted, treatment with these agents could precipitate diabetes (fasting plasma glucose (FPG) $\geq 126\text{mg/dL}$) in a patient with pre-diabetes ($100\text{mg/dL} \leq \text{FPG} < 126\text{mg/dL}$) or cause a non-diabetic ($\text{FPG} < 100\text{mg/dL}$) to be re-classified as having pre-diabetes.

1.8.2.6 Proposed Mechanisms of Second-Generation Antipsychotic-Induced Glucose Dysregulation

There are several hypotheses as to how the second-generation antipsychotics may induce glucose dysregulation. These include a direct toxic effect on pancreatic islet cell receptors, via inhibition of dopamine D₂ receptors or by antagonism of serotonin 5-HT_{1A} and 5-HT_{2A/C} receptors.¹⁵³ Alternatively, insulin resistance may arise due to treatment-induced weight gain and increases

in abdominal adiposity.¹⁵³ Weight gain is unlikely to be the sole etiology of glucose dysregulation induced by the second-generation antipsychotics, as glucose dysregulation has occurred in both the presence^{153;165;171} and absence of weight gain.^{190;193} Likewise, glucose dysregulation has been noted to resolve, in some cases rapidly, on discontinuation of the antipsychotic but without necessarily an accompanying decrease in weight. Irrespective of the mechanism by which glucose dysregulation occurs, it may have significant short and long-term sequelae for a patient's health.

1.8.2.7 Conclusion

While glucose dysregulation appears to be associated with the use of second-generation antipsychotic agents, it is difficult to ascertain the extent of the problem. Many of the studies conducted were limited by small sample sizes, absence of control groups, and an inability to confirm fasting blood glucose levels. Cohort studies have used varied eligibility criteria and methodologies with the result that the findings are conflicting. Although there are a limited number of well-controlled trials, these typically have restricted their inclusion criteria to patients with schizophrenia or schizoaffective disorder, and may have limited generalizability to other patients prescribed antipsychotic therapy. Of the second-generation agents, clozapine and olanzapine have been most frequently implicated to date; however, there is insufficient evidence to determine the differential propensities of the various agents. Glucose dysregulation appears to be independent of dose although the evidence is conflicting.

Four of the six second-generation antipsychotic agents (clozapine, olanzapine, risperidone and quetiapine) have been associated with weight gain. The research studies describing weight gain are poorly controlled and often reported idiosyncratically. Weight gain is hypothesized as a mechanism by which

these agents may induce glucose dysregulation; however, studies suggest it may be just one of the factors contributing to glucose dysregulation.

The correlation between second-generation antipsychotics and diabetes remains unknown. The increasing numbers of reports of glucose dysregulation following treatment initiation with the second-generation antipsychotic agents prompts concerns of a possible casual relationship. A diagnosis of diabetes does not preclude the use of second-generation antipsychotics nor does it contraindicate their continued use in patients who develop glucose dysregulation while on treatment. Judicious management of these patients using standard dietary interventions, weight control and the use of glucose regulating agents may be applied. In February 2004, an expert consensus panel issued recommendations on the management of patients treated with antipsychotics with regard to obesity and diabetes.²⁶¹ Baseline screening and routine follow-up monitoring is advocated for all patients commencing antipsychotic therapy. (Table 1.7)

Table 1.7: Protocol for Monitoring Patients on Second-Generation Antipsychotic Therapy*²⁶¹

Parameter	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal /Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood Pressure	X			X		X	
Fasting Blood Glucose	X			X		X	
Fasting Lipid Profile	X			X			X

* More frequent assessments may be required based on the clinical status of the patient

They recommend that patients with a high risk of diabetes at baseline, those who gain five percent or more weight from baseline at any time during therapy, or those who develop worsening glycemia while on antipsychotic therapy be treated with aripiprazole or ziprasidone, two agents, which to date have not been associated with significant weight gain or diabetes.²⁶¹ In making these recommendations, the expert panel acknowledged the deficits in the currently available research.²⁶¹ They emphasize the need for well controlled trials with adequate sample sizes to determine if there is a difference in the potential of the various second-generation agents to cause diabetes, so that the risks and benefits associated with the use of these agents can be more accurately assessed.

1.8.3 Dyslipidemia

Hyperlipidemia was first reported with clozapine in the mid-1990s.^{262;263} Subsequently, similar reports documented new-onset hypertriglyceridemia in patients treated with olanzapine.^{264;265} Using pooled data from short-term, placebo-controlled clinical trial reports, olanzapine, quetiapine and ziprasidone have ‘infrequently’ been associated with hypercholesterolemia, and additionally, in the case of quetiapine, hypertriglyceridemia.^{37;38;40} In post-marketing evaluation reports, risperidone was ‘rarely’ associated with hypertriglyceridemia.³⁹ In contrast, aripiprazole was not associated with medically important changes in triglyceride, HDL, LDL or total cholesterol levels in a 26-week placebo-controlled trial.³⁵

The findings from case studies and controlled trials have been confirmed in retrospective clinical studies. Using a nested case-control design, Koro et al. assessed the effect of olanzapine and risperidone on the risk of hyperlipidemia in patients with schizophrenia.²⁶⁶ Treatment with olanzapine was associated with a significant increase in odds of developing hyperlipidemia compared to those receiving no antipsychotic therapy, and to those treated with a first-generation

antipsychotic agent, with odds ratios of 4.65 (95% CI: 2.44-8.85) and 3.36 (1.77-6.39) reported, respectively.²⁶⁶ In contrast, regardless of comparator group, no such increase was noted with risperidone.²⁶⁶ Similarly, in a retrospective chart review assessing metabolic changes in patients during their first year of treatment, olanzapine was associated with significantly greater increases in serum triglycerides compared to risperidone (+88.2mg/dL versus +29.7mg/dL; $p=0.042$).²¹⁰ Fasting total cholesterol levels were also noted to increase significantly in the olanzapine cohort (+23.6mg/dL; $p<0.001$), but not in those treated with risperidone (+7.2mg/dL; $p=0.131$).²¹⁰ Increases in lipid parameters were not correlated with changes in weight parameters.²¹⁰

In a prospective 12-week review, olanzapine-associated increases in serum triglycerides (mean +60mg/dL; $p<0.04$) were found to correlate ($r = 0.484$; $p<0.02$) with changes in body weight.²⁶⁴ No increase in fasting blood cholesterol levels was noted.²⁶⁴ Of concern is the magnitude of increase in triglyceride levels, with an average increase of 37 percent from baseline fasting levels noted. Likewise, in a 12-month study, average increases of 48 percent and 35 percent in fasting triglyceride levels, respectively, were noted for male and female patients treated with clozapine.²⁶⁷ When compared to ziprasidone, significant increases in total cholesterol ($p<0.0001$), triglycerides ($p<0.003$), low-density lipoprotein (LDL) cholesterol ($p<0.0004$) and apoprotein B levels ($p<0.0001$) were noted with olanzapine in a double-blind, randomized controlled trial including patients with schizophrenia or schizoaffective disorder. Triglyceride levels increased by a median of 28mg/dL in the olanzapine group compared to a median decrease of 2mg/dL in the ziprasidone group in this brief six-week trial. High density lipoprotein (HDL) cholesterol levels were not significantly altered in this study.²⁵⁶

The exact mechanism by which the second-generation antipsychotics influence triglyceride metabolism is unknown. One hypothesis relates to the structural similarity between the agents associated with the most significant effects on triglyceride levels, clozapine, olanzapine and quetiapine, and the phenothiazine derivatives which have also been associated with this adverse effect.²⁶⁸ While weight gain is a risk factor for dyslipidemia, it has not been found to be consistently correlated with the development of dyslipidemia with the second-generation antipsychotics.^{210;264}

Dyslipidemia is of particular importance in patients with serious mental illness as many possess multiple risk factors for the development of coronary artery disease including high prevalence rates of smoking. Elevation of triglyceride levels to 400 to 500mg/dL or higher increases the risk of acute pancreatitis, a condition associated with increased morbidity and mortality. Dyslipidemia, specifically low HDL cholesterol or high triglyceride levels, is also an independent risk factor for diabetes.

1.8.4 Pancreatitis

In a report published by Koller et al., it was suggested that the second-generation antipsychotic agents clozapine, olanzapine and risperidone may precipitate pancreatitis.²⁶⁹ This is an inflammatory condition of the pancreas which may be acute or chronic.²⁷⁰ Acute pancreatitis is characterized by increased serum concentrations of pancreatic amylase and lipase and severe upper abdominal pain.²⁷⁰ The authors examined adverse drug reports for these agents in addition to haloperidol. Despite historically more extensive usage of haloperidol, it was associated with fewer reported cases of pancreatitis. Forty percent, 33 percent, 16 percent and 12 percent of the reports were for patients treated with clozapine, olanzapine, risperidone and haloperidol, respectively.²⁶⁹ Furthermore, 50 percent of patients who developed pancreatitis on haloperidol

were receiving concomitant therapy with a second-generation antipsychotic.²⁶⁹ Pancreatitis was accompanied by hyperglycemia, and less frequently acidosis, in some of the patients treated with the second-generation antipsychotics.²⁶⁹ In an acute attack of pancreatitis, the occurrence of hyperglycemia in excess of 200mg/dL is a marker for clinically severe disease.²⁷⁰ In patients with chronic pancreatitis, diabetes typically occurs as a late manifestation of the disease associated with calcification of the pancreas.²⁷⁰

Pancreatitis is a significant adverse effect in that it associated with considerable morbidity and/or mortality.²⁷⁰ Fifteen to twenty percent of patients die as a result of complications from an acute attack, with mortality rates of 50 percent reported within 20 to 25 years of diagnosis in patients with chronic pancreatitis.²⁷⁰ In particular, patients who are obese, or older, appear to be at increased risk of complications.^{269;270} In the series reported by Koller et al., 22 of the 192 patients died as a result of pancreatitis, with death most frequently associated with clozapine (N=7) and olanzapine (N=9).²⁶⁹ Pancreatitis did not appear to be a dose-related effect, and the majority of cases occurred within six months of initiating antipsychotic treatment.²⁶⁹ Of note, alcohol abuse is a risk factor for pancreatitis and accounts for approximately 40 percent of acute, and 70 percent of chronic cases in the U.S..²⁷⁰ Substance abuse is commonly reported among patients with schizophrenia and bipolar disorder, although it was not present as a comorbidity in at least 20 percent of the patients in this case series.^{22;27;58;269} Valproic acid has additionally been associated with pancreatitis, and was prescribed as a concomitant medication in 23 percent of the patients.^{269;270} The authors postulated, however, that as many of these patients had been treated long-term with valproate without undue effect, that antipsychotic therapy had acted to augment the toxicity of valproate to the

pancreas.²⁶⁹ In post-marketing surveillance reports, aripiprazole and quetiapine have rarely been associated with pancreatitis.^{35;38}

In summary, although rarely reported with the first-generation antipsychotics, there appears to be a surfeit of reports of pancreatitis associated with the second-generation agents, with clozapine and olanzapine most frequently implicated. This has implications for the selection of antipsychotic therapy in the seriously mentally ill, given the prevalence of additional risk factors for pancreatitis or its consequences, including alcohol abuse, valproate use and obesity in this cohort.

1.8.5 Hyperprolactinemia

Elevated plasma prolactin levels are commonly reported in patients treated with first-generation antipsychotic agents.^{24;271;272} It results from the action of these agents as dopamine D₂ receptor antagonists in the tuberinfundibular tract, leading to increased prolactin secretion from the anterior pituitary.²⁷² The second-generation agents also inhibit dopamine D₂ receptors but to a lesser extent than the first-generation agents.²⁴ Among the second-generation antipsychotics, prolactin levels may be elevated by variable amounts. Risperidone is reported to cause significant increases in prolactin, with increases in serum prolactin levels of 45 to 80 ng/mL reported (normal prolactin levels: <20ng/mL).²⁷² This effect appears to be dose-related, to affect both men and women, and to persist with chronic treatment.²⁷² In contrast, aripiprazole, clozapine and ziprasidone have not been associated with sustained increases in prolactin levels.^{35;36;271;272} The effect of olanzapine is equivocal with both decreases and moderate increases (1-4ng/mL) in prolactin levels reported.²⁷² Any hyperprolactinemia appears to be dose-related, occurring when doses of olanzapine in excess of 20 milligrams a day are used.^{271;272} Switching patients to olanzapine has also been reported to reverse risperidone-induced

hyperprolactinemia without loss of treatment efficacy.²⁷¹ Differences in the effect of antipsychotic agents on prolactin levels is thought to relate to their differential binding properties on pituitary D₂ receptors.²⁷³ With the exception of risperidone and high dose olanzapine, the threshold for achieving sustained D₂ inhibition in the pituitary, and consequent increased prolactin levels, is not reached by the second-generation antipsychotic agents.^{272;273}

Adverse systemic effects associated with increased prolactin levels include: galactorrhea, amenorrhea, infertility, acne and hirsutism in women; gynecomastia in men; and sexual dysfunction in both men and women.^{24;271;272} It has been proposed that women experiencing amenorrhea may be at increased risk of osteoporosis and cardiovascular events secondary to estrogen deficiency²⁷⁴. Hyperprolactinemia has also been associated with an increased risk of breast cancer, although the evidence is conflicting.²⁷¹

Symptomatic patients may be managed by switching to an agent not associated with an appreciable sustained effect on prolactin, such as aripiprazole, olanzapine, quetiapine or ziprasidone.²⁴ Alternatively, dopamine receptor agents such as bromocriptine or amantadine may be used, although there is a possible risk of psychotic relapse.²⁴ Combined oral contraceptives may be effective in women with secondary amenorrhea to reverse the symptoms associated with estrogen deficiency, including loss of bone mineral density and osteoporosis.²⁷¹

1.9 Section 7: Diabetes Mellitus

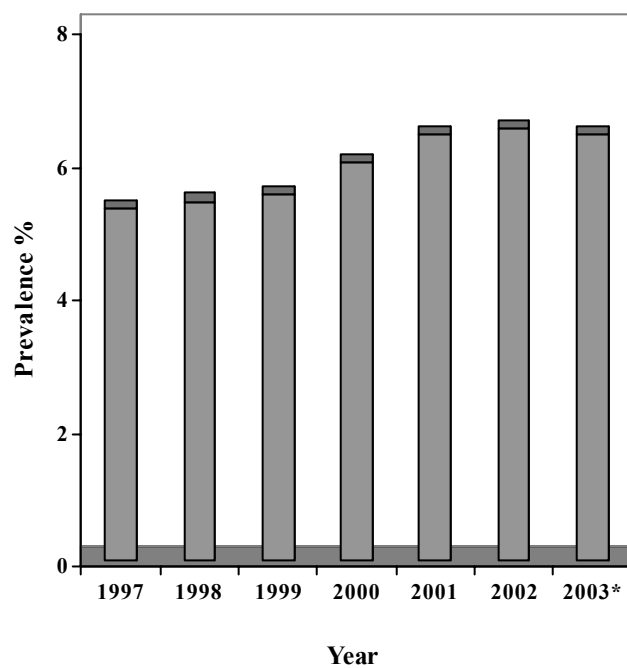
A brief overview of the epidemiology, etiology and classification of diabetes mellitus will be provided in this section. The proposed association between diabetes mellitus and mental health illnesses will be discussed. In addition, some of the difficulties associated with diagnosing and managing a chronic health condition, such as diabetes, in patients with serious mental health disorders will be highlighted.

1.9.1 Epidemiology

Diabetes Mellitus (hereafter referred to as diabetes) has been described as a “group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.”²²⁴ The estimated prevalence of diabetes among U.S. adults was 8.7 percent (13 million) in 2002, of whom approximately 29 percent (five million) were undiagnosed.²²⁴ As illustrated in Figure 1.1 (page 91), there has been a worrying increase in the prevalence of diabetes in the U.S. in recent years, from an age-adjusted prevalence of diagnosed diabetes of 5.3 percent in 1997, to 6.4 percent in 2003.²⁰² The prevalence of diabetes is dependent on age, with adults aged 65 years or older twice as likely to have diabetes compared to those aged between 45 and 54 years. (Figure 1.2, page 92) ²⁰² The prevalence of diabetes also varies by race/ethnicity. In 2002, among adults with diagnosed diabetes, non-Hispanic blacks were 1.6 times as likely, and Hispanic/Latino Americans 1.5 times as likely to have diabetes as non-Hispanic white adults of similar age. (Figure 1.3, page 93) ²⁰¹ Among the largest Hispanic-Latino subgroup, Mexican Americans, the risk of diabetes is two-fold that of non-Hispanic whites of a similar age.²⁰¹ The highest prevalence of diagnosed diabetes occurs in American Indians and Alaskan Natives; of those receiving care from the Indian Health Service, 14.9 percent

have been diagnosed with diabetes.²⁰¹ The prevalence of pre-diabetes has been estimated to be 12 million (22.6%) among overweight adults aged 45 to 74 years. This number is expected to be considerably higher if expanded to all overweight individuals aged 18 years or older.²⁷⁵ In 2000, over 1 million adults aged 18 to 79 years in the U.S. were newly diagnosed with diabetes. Consistent with prevalence trends, the incidence of diabetes is dependent on age and race/ethnicity with a higher incidence noted among older adults, blacks and Hispanics. The highest incidence of diagnosed diabetes is among men aged 65-79 years with 14.5 cases per 1,000 population reported in 2001, compared to 9.4 cases per 1,000 population among women of the same age.²⁷⁶

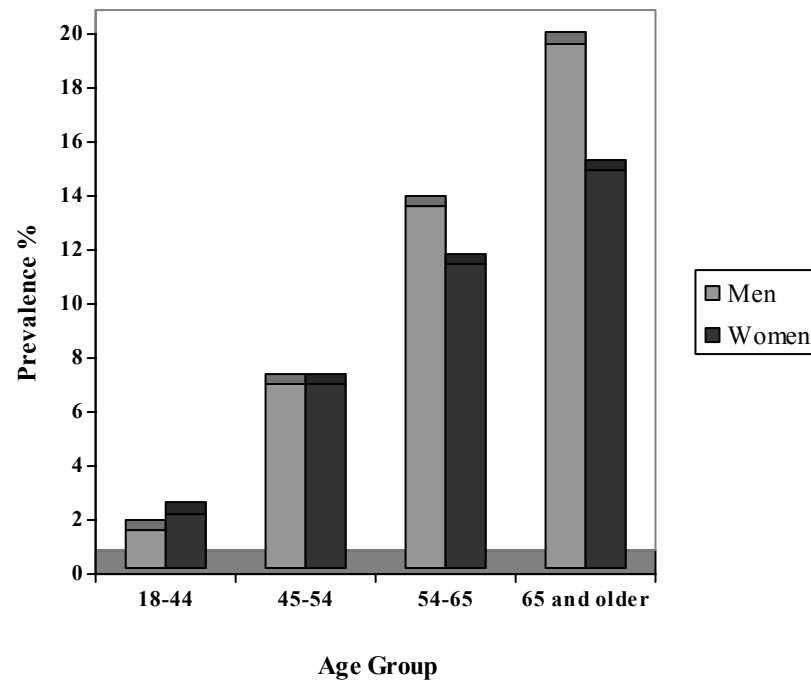
**Figure 1.1: Age-Adjusted Prevalence¹ of Diagnosed Diabetes
Among Adults Aged 18 years or Older: U.S., 1997-2003***



* Data from January –September 2003²⁰²

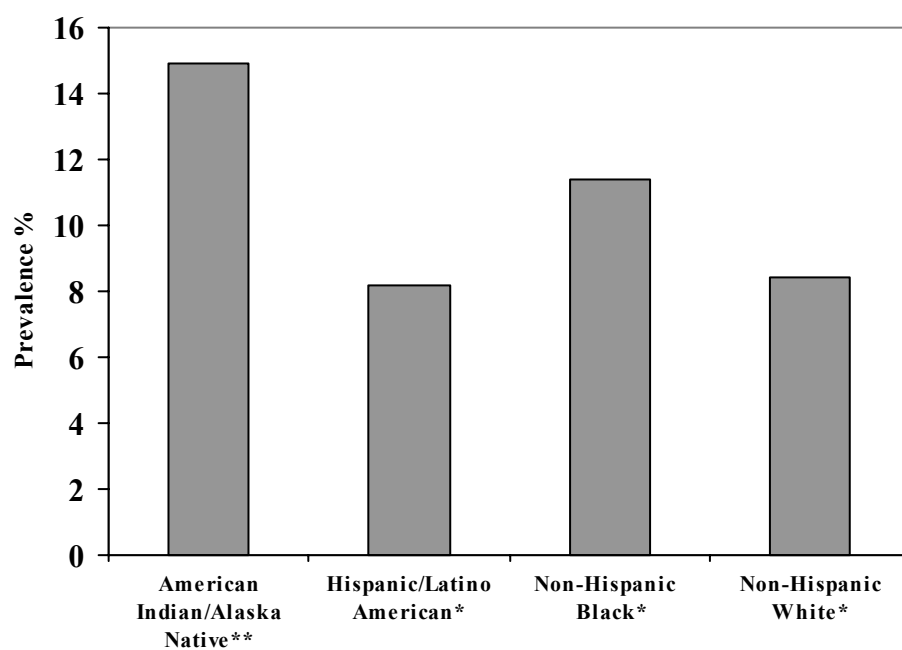
¹ Prevalence of diabetes is based on self-reported of ever being diagnosed with diabetes.

Figure 1.2: Prevalence of Diagnosed Diabetes Among Adults Aged 18 Years and Older, by Age Group and Gender: U.S., 1997-2003*



* Data from January –September 2003²⁰²

Figure 1.3: Age-Adjusted Prevalence of Diagnosed Diabetes Among Adults Aged 20 years or Older, by Race/Ethnicity: U.S., 2002



* Data for Hispanic/Latino American, Non-Hispanic black and Non-Hispanic white populations extrapolated from National Health Interview Survey (1999-2001) and National Health and Nutrition Examination Survey (1999-2000) data.

** Data for American Indians /Alaska Natives based on prevalence of diabetes in those receiving outpatient care in 2002 from the Indian Health Service.²⁰¹

1.9.2 Classification

The majority of patients are categorized as either Type 1 diabetics (5 to 10%) or Type 2 diabetics (90 to 95%).²⁰⁴ Type 1 diabetes is caused by an absolute deficiency of insulin secretion and Type 2 diabetes by a combination of insulin resistance and inadequate insulin secretory response.²⁰⁴ Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are terms used to describe patients with plasma glucose levels that are elevated, but not diagnostic of diabetes.²⁰⁴ These patients are, however, classified as ‘pre-diabetes,’ as approximately 25 percent of these patients proceed to frank diabetes.²⁰⁴ In 2003, the criteria for the diagnosis of diabetes was revised, and are shown below in Table 1.8.²⁷⁷ As illustrated, there are three possible ways in which diabetes may be diagnosed, each of which requires confirmatory testing on a subsequent day in the absence of unequivocal hyperglycemia.²⁷⁷

Table 1.8: Criteria for the Diagnosis of Diabetes Mellitus²⁰⁴

-
1. Symptoms of diabetes plus casual plasma glucose concentration $\geq 200\text{mg/dL}$. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria; polydipsia; and unexplained weight loss.
 - Or
 2. FPG $\geq 126\text{mg/dL}$. Fasting is defined as no caloric intake for at least 8 hours.
 - Or
 3. 2-hour postload glucose $\geq 200\text{mg/dL}$ during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure is not recommended for routine, clinical use.

Abbreviations: FPG – Fasting plasma glucose; OGTT – Oral glucose tolerance test;
WHO – World Health Organization

It has been recommended that a fasting plasma glucose of $\geq 126\text{mg/dL}$ be used to determine the incidence and prevalence of diabetes in epidemiological studies.²⁷⁷ Although this is expected to lead to an underestimation of the prevalence of diabetes compared to the use of oral glucose tolerance tests, it serves to standardize and facilitate such studies.²⁷⁷

The ICD-9 codes specified for diabetes mellitus are 250.1x to 250.99 with category designation based on the presence, or absence, of complications such as ketoacidosis, renal, ophthalmic or neurological complications. Further specifiers are used to categorize patients according to diabetes type (1 or 2), and to the level of control attained (uncontrolled or not stated to be uncontrolled). A new ICD-9 code of 277.7 has recently been assigned to the insulin resistance syndrome so that patients with this condition can be captured in future studies.

1.9.3 Etiology

Type 1 diabetes is an immune-mediated condition resulting in destruction of β -cells and absolute insulin deficiency.²⁰⁴ Patients typically present as children or young adults. Risk factors include autoimmune, genetic and environmental factors.²⁰⁴ Type 2 diabetes is a condition associated with insulin resistance and relative insulin deficiency.²⁰⁴ It is viewed as a polygenic disorder that develops when a diabetogenic lifestyle is superimposed on a genetic susceptibility. The majority of patients are obese or have increased abdominal adiposity.²⁰⁴ As noted previously, the prevalence of diabetes increases with age and is more prevalent in certain racial or ethnic groups.²²⁴ In addition to a BMI of 25Kg/m^2 or more, other risk factors for diabetes include: a family history of diabetes; sedentary lifestyle; hypertension; dyslipidemia (low HDL cholesterol and/or a high triglyceride level); a history of gestational diabetes or delivery of a baby weighing over nine pounds; polycystic ovarian disease; a history of vascular disease; and previously

identified IFG or IGT.²²⁴ The impact of weight gain / obesity and drug-induced diabetes will now be discussed in detail.

1.9.3.1 Obesity

The prevalence of obesity among U.S. adults aged 20 years and older has increased considerably in recent years from 19.4 percent in 1997 to 23.9 percent in 2002.²⁰² When adjusted for age, 64.5 percent of U.S. adults aged 20 years or older were classified as overweight (BMI 25-29.9 Kg/m²) and 30.5 percent as obese (BMI \geq 30Kg/m²), in 1999-2000.²⁷⁸ Excess weight is associated with an increased incidence of type 2 diabetes in addition to other diseases such as cardiovascular disease, dyslipidemia, hypertension, stroke, and certain cancers.²⁷⁹ Specifically, the prevalence of type 2 diabetes increases with increasing severity of overweight and obesity.²⁷⁹ For example, the prevalence increases from 2.03 percent for normal weight males (BMI 18.9 – 24.9Kg/m²) to 10.65 percent for males with a BMI \geq 40Kg/m² and from 2.38 percent for normal weight females to 19.89 percent for females with a BMI \geq 40Kg/m².²⁷⁹ Among patients with diabetes, the age-adjusted prevalence of obesity was 46.1 percent in 2002, with 80.5 percent reported to be overweight.²⁸⁰ In data from the Nurse's Health study, Colditz et al. reported that women who gained more than 5-7.9Kg as adults were 1.9 times (95% CI: 1.5 to 2.3) more likely to develop type 2 diabetes than women who maintained a stable weight (those who gained, or lost less than 5Kg) from the age of 18 years.²⁸¹ Larger increases in weight were associated with even higher relative risks: women who gained 8.0 – 10.9Kg and those who gained in excess of 20Kg were 2.7 (95% CI: 2.1 to 3.3) and 12.3 (95% CI: 10.9 to 13.8) times more likely to develop type 2 diabetes , respectively.²⁸¹ When translated into a change in BMI, weight gain of one BMI unit has been found to correspond to a 2.9 to 4.3 increase in relative risk of diabetes in women, and an increase in risk of 1.0 to 1.5 in men.^{281;282}

1.9.3.2 Drug-Induced Diabetes Mellitus

Certain drugs have been implicated in the development of diabetes. These drugs typically impair insulin secretion thereby precipitating diabetes in susceptible individuals.²⁰⁴ The effect of most of these drugs is reversible on their discontinuation.²⁰⁴ The most commonly implicated agents include: glucocorticoids; thyroid hormones; thiazides; diazoxide; phenytoin; β -adrenergic agonists; nicotinic acid; and α -interferon.²⁰⁴ More recently, an association between the use of second-generation antipsychotics and diabetes has been proposed.²⁰ This has been assumed to be a class-related effect, although aripiprazole and ziprasidone have yet to be directly implicated.²⁰ Compared to patients not receiving antipsychotic therapy, a relative risk of developing diabetes of 3.3 to 4.7 has been described for the second-generation agents.^{4;10} The proposed link between the second-generation antipsychotics and diabetes is described more fully in section 6.

1.9.4 Course

Although type 1 diabetics can present at any age, patients typically present before the age of 20 years.²⁸³ Patients are typically thin and prone to developing diabetic ketoacidosis.²⁸³ Type 2 diabetes, previously known as adult onset diabetes is the most prevalent form of diabetes, and is increasingly being reported in younger patients including children and adolescents.²⁰⁴ As stated, the risk of type 2 diabetes increases with age, obesity and lack of physical activity, particularly in patients with a genetic susceptibility. The symptoms and consequences of chronic hyperglycemia and hyperglycemic crises will be discussed in this section.

1.9.4.1 Chronic hyperglycemia

In general, patients with type 1 diabetes present at a young age with acute symptoms of diabetes and markedly elevated blood glucose levels.²⁸⁴ In contrast, patients with type 2 diabetes frequently go unrecognized for long periods, as progression to overt hyperglycemia may be slow, and patients are typically asymptomatic at the early stages.²⁰⁴ Patients may often present without symptoms although others present with advanced complications, particularly retinopathy and neuropathy.²⁸³ Symptoms of marked hyperglycemia include: polyuria; polydipsia; polyphagia; fatigue; blurred vision; and weight loss.²⁰⁴ Chronic hyperglycemia may lead to increased susceptibility to certain infections and growth impairment in children.²⁰⁴ The morbidity and mortality associated with diabetes primarily relate to chronic complications of the disease including: retinopathy; nephropathy; neuropathy; and an increased incidence of atherosclerotic cardiovascular, peripheral vascular and cerebrovascular disease.²⁰⁴ Seventy-five percent of deaths in patients with diabetes are due to cardiovascular events.²⁸³ The morbidity and mortality associated with diabetes is increased further in patients who smoke due to an increased risk of microvascular and macrovascular complications.²⁸⁵ In particular, smoking impacts on the development and progression of microalbuminuria, renal impairment and neuropathy.²⁸⁵ There are equivocal findings on the association between retinopathy and smoking.²⁸⁵ Diabetics who smoke have an increased risk of coronary artery disease and stroke and have increased mortality from coronary heart disease.²⁸⁵

1.9.4.2 Hyperglycemic Crises

Acutely, diabetic patients may experience hyperglycemia with ketoacidosis or hyperosmolar hyperglycemia, both of which may be life-threatening.²⁸⁶ The annual incidence of diabetic ketoacidosis is estimated to be

between 4.6 and 8 cases per 1,000 diabetic patients.²⁸⁶ Hyperosmolar hyperglycemia syndrome is rare, and accounts for less than one percent of primary diabetic hospital admissions in epidemiological studies.²⁸⁶ Type 1 diabetics are prone to developing diabetic ketoacidosis with 20 to 40 percent of these patients actually initially presenting in diabetic ketoacidosis.²⁸³ Typically, both conditions are rare in patients with type 2 diabetes and only occur secondary to a stressor such as infection.²⁰⁴ Both diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome are difficult to manage and are associated with mortality rates of approximately five percent and 15 percent, respectively, in experienced settings.²⁸⁶ Patients present with a history of polyuria, polydipsia, polyphagia, weight loss, gastrointestinal symptoms such as abdominal pain (diabetic ketoacidosis only), vomiting, dehydration, and weakness.²⁸⁶ Changes in mental status occur and are progressive with increasing severity of the condition, varying from mental alertness to profound lethargy to stupor or coma in patients with severe diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome.²⁸⁶

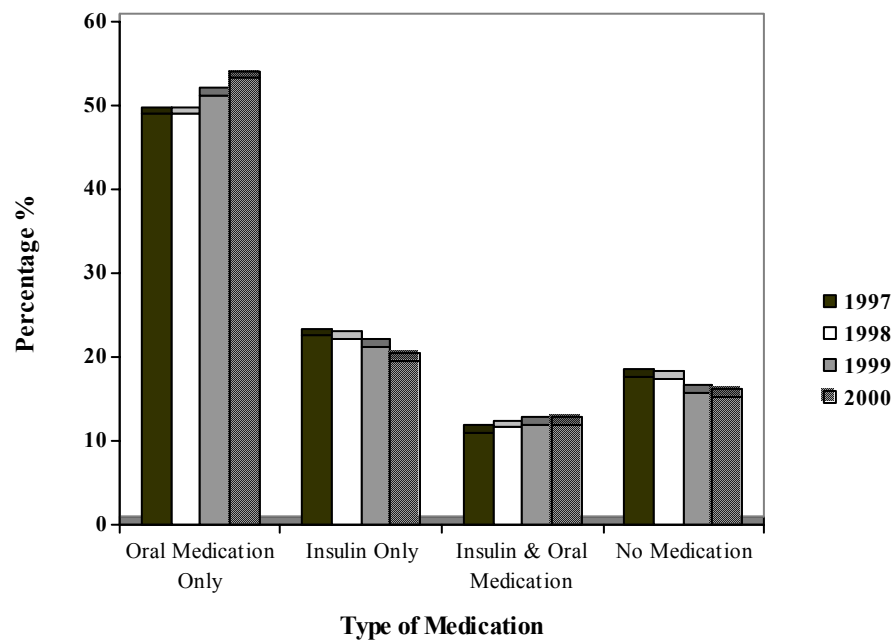
The second-generation antipsychotics clozapine, risperidone and olanzapine, have been associated with a worrying number of cases of diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome.^{5;8;269} As noted, the presence of diabetic ketoacidosis with type 2 diabetes is rare and typically a marker of severe metabolic stress. Ketosis usually occurs only in those with impaired insulin secretion due to decreased pancreatic insulin reserve. This may reflect difficulties in the early recognition of symptoms of hyperglycemia in patients with serious mental health disorders, or inappropriate classification of these symptoms as medication-related adverse effects. Alternatively, it may be due to an increased prevalence of other risk factors for hyperglycemic crises in patients taking these agents. Alcohol abuse is a known precipitating factor for hyperglycemic crises in diabetes.²⁸⁶ It is also a common comorbidity in patients

with schizophrenia and bipolar disorder with estimated prevalence rates of 33.7 percent and 43 percent reported, respectively.^{52;56} In addition, pancreatitis, another known precipitant of hyperglycemic crises, has been described with the second-generation antipsychotic agents.²⁶⁹

1.9.5 Diabetes Management

Patients with type 1 diabetes have absolute insulin deficiency; therefore, requiring insulin therapy, by injection or pump, to survive. Patients with type 2 diabetes may initially be managed by lifestyle modifications alone, using a combination of weight loss, diet control and exercise. Most patients progress to requiring additional treatment with oral hypoglycemic agents and/or insulin sensitizing agents or insulin therapy. In 2000, among patients diagnosed with diabetes, 10 million patients (84.8%) reported using a diabetic medication, an increase from 8.4 million (82.3%) in 1997.²⁸⁷ The majority of patients reported using oral medication only (53.3%). (Figure 1.4, page 101) ²⁸⁷ As illustrated in Table 1.9 (page 102), there are five classes of oral medication licensed by the FDA in addition to insulin for the management of type 2 diabetes: α -glucosidase inhibitors; biguanides; meglitinides; sulfonylureas and thiazolidinediones. These agents are disease specific for type 2 diabetes, with limited off-label use of these agents for other conditions. However, new treatment indications and expanded use of these agents is likely in the future for other conditions including diabetes prevention and insulin resistance syndrome.

Figure 1.4: Percentage of Adults Diagnosed with Diabetes Reporting Use of Diabetes Medication, by Type of Medication, U.S., 1997-2000*



* Estimates based on number of patients reporting a diagnosis of diabetes and use or non-use of medications for diabetes in the NHIS and NCHS. Given the high estimated prevalence of patients with undiagnosed diabetes, the chart underestimates the percentage of patients on no medication.²⁸⁷

Table 1.9: Oral Agents Licensed for the Management of Type 2 Diabetes Mellitus ^{288;289}

Agent	Recommended Daily Dose (mg)	Strengths Available (mg)	Off-Label Indications
A-Glucosidase Inhibitor			
Acarbose	75-300	50, 100	T2DM prevention; Dumping Syndrome; T1DM
Miglitol	75-300	25, 50, 100	
Thiazolidinediones (PPAR-γ Agonists)			
Pioglitazone	15-45	15, 30, 45	Insulin resistance ¹ ; PCOS; Non-alcoholic steatohepatitis; Werner syndrome
Rosiglitazone	2-8	2, 4, 8	Insulin resistance ² ; HAART-associated lipodystrophy; Non-alcoholic steatohepatitis; Metabolic syndrome; PCOS; ISR ³
Sulfonylureas			
Acetohexamide	250-1,500	250,500	Neurogenic diabetes insipidus
Chlorpropamide	100-500	100, 250	
Glimepiride	1-8	1, 2, 4	Reverse diabetic microangiopathy; Gestational DM
Glipizide	2.5-40	5, 10,	
Glipizide-GITS (XL)	2.5-20	2.5, 5, 10	
Glyburide	2.5-20	1.25, 2.5, 5	
Glyburide micronized	3-12	1.5, 3, 4.5, 6	
Tolbutamide	250-3,000	500	Prophylaxis gestational DM; Obesity; T2DM prevention; PCOS
Tolazamide	100-1,000	100, 250, 500	
Biguanide			
Metformin	500-2,550	500, 850, 1,000, 500 XR	
Meglitinide			
Repaglinide	0.5-16	0.5, 1, 2	
Nateglinide	180-360	60, 120	

Abbreviations: mg – milligrams; T1DM – Type 1 Diabetes Mellitus; T2DM – Type 2 Diabetes Mellitus; DM – Diabetes Mellitus; HAART – Highly Active Antiretroviral Therapy; PCOS – Polycystic Ovarian Syndrome; ISR – In-stent restenosis

¹. Decrease insulin resistance in stroke patients

². Decrease insulin resistance in non-diabetic patients receiving continuous ambulatory peritoneal dialysis (CAPD)

³. Decrease in-stent restenosis in type 2 diabetic patients with coronary artery disease

1.9.6 Economic Burden

As evident, there are high rates of morbidity and mortality associated with diabetes. In fact, diabetes is the fifth leading cause of death by disease in the U.S.²⁹⁰ In 2002, it was estimated that diabetes cost the U.S. \$132 billion between direct medical costs and lost productivity.²⁹⁰ This represents a staggering increase of 35 percent from the previous estimate of \$98 billion five years previously in 1997.²⁹⁰ These estimates exclude undiagnosed cases of diabetes and, therefore, underestimate the true burden of the disease.²⁹⁰ If current prevalence rates remain unchanged, this estimate is expected to further increase to \$156 billion by 2010 given an aging population in the U.S. that is increasing in size and racial and ethnic diversity.²⁹⁰ However, the future cost of diabetes is likely to be higher given the trend toward an increasing prevalence of diabetes and obesity in the U.S.

1.9.7 Diabetes and Mental Disorders

While the second-generation antipsychotics have been associated with the development of diabetes, this picture is confused by a number of factors. Specifically, do people with serious mental illness have a genetic predisposition to developing diabetes? Additionally, are patients with serious mental illness more likely to have a diabetogenic lifestyle compared to the general population? Complicating the picture further are the difficulties associated with the diagnosis and recognition of symptoms of diabetes in patients with serious mental illness. These issues will be discussed in brief here.

1.9.7.1 Predisposition of Patients with Schizophrenia and Affective Disorders to Diabetes

Limited data suggest that impaired glucose tolerance and diabetes mellitus are more common among patients with schizophrenia and bipolar

disorder than the general population.^{13;14} While antipsychotic agents have been implicated in the development of diabetes, additional mechanisms have been proposed. These are supported by retrospective case studies, most of which predate the widespread availability of the second-generation antipsychotic agents. Additional support is provided by a clinical study that examined insulin resistance and diabetes in treatment naïve patients. A brief description of these studies is provided.

1.9.7.1.1 Diabetes Prevalence Studies

An Italian retrospective study of 95 chronic schizophrenic patients aged 45 to 74 years reported an overall prevalence of diabetes of 15.8 percent (95% CI: 12.1 to 19.5%) which was substantially higher than the reported prevalence of known diabetes of 2.1 to 3.2 percent in the general adult population.¹⁴ In all cases, onset of psychosis preceded the onset of diabetes by many years.¹⁴ In a U.S. study by the Schizophrenia Patients Outcomes Research Team (PORT), comorbidity from schizophrenia and diabetes mellitus was examined using a combination of three databases: patients enrolled in Medicaid (N=6,066); patients enrolled in Medicare (N=14,182); and patients from a field research study (N=719).¹³ The prevalence of diabetes in these schizophrenia patients was contrasted with the prevalence of diabetes in the general population, as measured by National Health Interview Survey (NHIS) data. The Medicaid and Medicare data were from 1991, when only clozapine was licensed for use, and, therefore, predates the widespread use of the second-generation antipsychotics. In the field study sample, (mean age 43 years), the rates of lifetime and current diabetes were 14.9 percent and 10.8 percent, respectively. These rates were consistent with the Medicaid and Medicare database results and far exceeded that of an age-matched general U.S. population (Table 1.10).¹³

Table 1.10: Prevalence of Diabetes in Schizophrenia Patients Enrolled in Medicaid and Medicare Compared to the General U.S. population (NHIS Cohort), Stratified According to Age ¹³

Sample	18 to 44 years (%)	45 to 64 years (%)
Medicaid ^a	6.7	18.8
Medicare ^a	5.6	14.9
NHIS ^b	1.2	6.3

^a 1991 Data

^b 1994 National Health Interview Survey

The study concluded that rates of diagnosed diabetes in schizophrenia patients exceeded those reported by the general population well before the widespread availability and use of the second-generation antipsychotic agents. Furthermore, consistent with trends observed in the general population, there was an increased prevalence of diabetes in women, African-Americans and older patients.¹³ In contrast, Regenold et al. noted a similar prevalence of diabetes in a group of hospitalized patients with schizophrenia to that expected in the general U.S. population, after adjusting for age, race and gender.¹⁵ They did however note significantly higher rates of diabetes among schizoaffective and bipolar patients compared to national norms.¹⁵ Similar trends have been noted for other patients with serious mental illness. In a small retrospective study published in 1986, McKee et al. noted a 2.5 fold increased prevalence of diabetes among hospitalized patients with psychosis compared to the general population.²⁹¹ Cassidy et al. documented a three-fold increase in the prevalence of diabetes in hospitalized patients with bipolar disorder compared to the general U.S. population, after adjusting for age, weight and race.¹⁸ One hypothesis for an association between diabetes and bipolar disorder relates to plasma cortisol levels. Glucocorticoid therapy has been noted to induce diabetes, similarly, hypercortisolemia has been reported during both manic and depressive episodes.¹⁸

1.9.7.1.2 Clinical Studies

Support for the hypothesis that schizophrenia and diabetes are associated independent of medication use, comes from a small prospective study that compared drug-naïve, first episode schizophrenia patients to a healthy control group. After matching for smoking and physical exercise habits, higher levels of glucose, insulin and cortisol were documented in the schizophrenia group, together with an increased likelihood of diabetes and impaired glucose tolerance.¹⁷ These findings were refuted by a small prospective study that contrasted schizophrenia patients that were currently antipsychotic-free with first-episode, antipsychotic-naïve patients. The authors concluded that while previous antipsychotic treatment may induce significant changes in insulin resistance, insulin secretion and leptin levels, these changes were not due to pre-existing impairment of glucose metabolism.²⁹²

1.9.7.1.3 Genetic Studies

Support for a genetic predisposition comes from a study that documented an inflated prevalence of diabetes of 18 to 30 percent in family members of patients with schizophrenia.²⁹³ This rate is similar to that reported by known diabetic patients, and greatly exceeds that of the general U.S. population.

1.9.7.2 Depression

The prevalence of comorbid depression has been noted to be increased approximately two-fold in patients with diabetes compared to the general population.²⁹⁴ Whether this indicates a susceptibility of patients with depression to develop diabetes, or rather reactive depression occurring secondary to a chronic illness is not known. Typically it is proposed that patients with chronic illnesses such as diabetes are at an increased risk of reactive depression. Limited data suggest however that patients with moderate or severe depression have an

approximately two-fold increased risk of developing diabetes after controlling for established risk factors for diabetes.²⁹⁵⁻²⁹⁷ Apart from the depressive disorders major depressive disorder and bipolar disorder, comorbid depression is common in schizophrenia and in patients with dementia-related psychological and behavioral problems.^{52;100} Regardless of the causal direction, patients with comorbid depression and diabetes have decreased glycemic control and increased risk of diabetic complications.²⁹⁸ This may contribute to the higher mortality rates seen in patients with comorbid mental illness and diabetes than the general diabetic population. Alternatively, the excess morbidity and mortality may reflect complications of an additional disease burden or poorer quality medical care in a vulnerable population. Any factor that increases the risk of diabetes in patients with mental disorders could further compound an existing problem.

1.9.7.3 Dementia

There is conflicting evidence as to the association between diabetes and both vascular dementia and Alzheimer's disease. Patients with diabetes have a high risk of underlying vascular disease, which may increase the risk of vascular dementia in these patients.²⁹⁹ Similarly, hypertension and hyperlipidemia, both known risk factors for diabetes are also risk factors for the development of vascular dementia.²⁹⁹ The relationship between diabetes and Alzheimer's disease is less straightforward. Researchers have hypothesized that hyperinsulinemia is associated with the development of islet amyloid and brain amyloid in patients with diabetes and Alzheimer's disease, respectively.³⁰⁰ In a longitudinal analysis of 683 people without dementia for 5.4 years, hyperinsulinemia was associated with an increased risk of incidence Alzheimer's disease (HR: 2.1, 95% CI: 1.5-2.9) and of all dementia (1.9, 95% CI: 1.4-2.7).³⁰⁰ The association between Alzheimer's disease and hyperinsulinemia remained unchanged even after adjusting for diabetes and known risk factors for diabetes such as BMI, age,

hypertension and LDL levels.³⁰⁰ Equivocal results have been reported however regarding the prevalence of Alzheimer's disease in patients with diabetes, with reports of increased,³⁰¹⁻³⁰³ decreased^{304;305} and comparable prevalence rates to the general population.³⁰⁶ A number of factors have been suggested to confound this relationship including the association of lower BMI and lower exercise rates in patients with Alzheimer's disease, which would increase, or decrease the risk of diabetes, respectively.²⁹⁹ Alternatively, the premature mortality associated with diabetes could obscure subsequent development of Alzheimer's disease.²⁹⁹ Another possible confounding factor is the possibility that patients with Alzheimer's disease may be less aggressively investigated and treated than those with other disease states, including vascular dementia. In a large population-based study by Gambassi et al., the patterns of drug use among nursing home residents with Alzheimer's disease and vascular dementia were examined.³⁰⁷ Overall, the researchers found a lower prevalence rate of comorbid diseases in those with Alzheimer's disease.³⁰⁷ After adjusting for demographic variables and the prevalence of comorbid disease, patients with Alzheimer's disease had a lower drug use than those with vascular dementia.³⁰⁷ Of note, the prevalence of diabetes was significantly higher among those with vascular disease than those with Alzheimer's disease (15% vs. 12%, $p<0.01$), although there was no difference in the use of anti-diabetic medications, after adjusting for demographic variables and the prevalence of comorbid disease.³⁰⁷

Unlike schizophrenia and bipolar disorder which appear to predispose patients to the development of diabetes, it is the presence of diabetes or hyperinsulinemia which may increase the risk of dementia. Regardless, patients with dementia may be systematically different to the general population with regard to insulin levels and occurrence of diabetes. The use of antipsychotic agents in patients with possible pre-existing diabetes may serve to exacerbate the

situation and to increase the apparent relative risk of hyperglycemia associated with these agents.

1.9.7.4 Diabetogenic Lifestyles

As described earlier, diabetes occurs when a diabetogenic lifestyle is superimposed on a diathesis for diabetes. It has been estimated that 25 percent of insulin resistance is secondary to obesity, 25 percent secondary to inactivity and the remaining 50 percent due to genetic factors.³⁰⁸ While the burden of weight gain secondary to neuroleptic and psychotropic agents is well documented, patients with serious mental illness have also been documented to engage in fewer health-promoting behaviors than their counterparts in the general population.^{309;310} In particular, they are documented to smoke more, exercise less frequently, and eat less healthy diets.^{309;310} These lifestyle differences further increase the risk of overweight and obesity in this community and, therefore, of conditions including diabetes. A brief overview of these factors will now be provided.

1.9.7.4.1 Body Mass Index and Weight in Schizophrenia Patients

The association between body mass index (BMI) and weight gain in the pathogenesis of type 2 diabetes was outlined in section 6. Patients with schizophrenia tend to have higher levels of obesity than their counterparts in the general population as evidenced by a study by Homel et al., who conducted a retrospective study examining the change in BMI for individuals with, and without schizophrenia between 1987 and 1996.¹⁴⁰ During this period, the use of the second-generation antipsychotic agents increased. The mean BMI for patients was found to be significantly higher for individuals with schizophrenia compared to those without (28.0Kg/m^2 vs. 25.7Kg/m^2). After stratifying according to gender, a significant difference was noted only for females (30.3Kg/m^2 vs. 25.5Kg/m^2).¹⁴⁰ Whereas between 1987 and 1996 a trend towards an increase in

BMI was noted for the non-schizophrenia population, there was little evidence of such a trend among patients with schizophrenia. When the data were stratified according to age and gender, a significant increase ($p<0.001$) in BMI was noted for young females (18 to 30 years) with schizophrenia relative to their non-schizophrenia counterparts, causing a much higher obesity rate in this group in recent years.¹⁴⁰ In a similar study in Germany, Theisen et al., documented prevalence rates of obesity among men and women with schizophrenia that were 5.1 and 6.4 times, respectively, that of the German reference population.¹⁴¹ This trend was exacerbated among patients chronically treated with the second-generation antipsychotic agents with obesity prevalence rates of 64 percent for clozapine, 56 percent for other second-generation agents (amisulpiride, olanzapine, risperidone), 30 percent for first-generation antipsychotics and 28 percent for patients that were currently antipsychotic free.

Using data from the National Health Interview Survey (NHIS) and the National Health and Nutrition Interview Examination Survey III (NHANES III), Allison et al. documented similar trends.¹⁴² In the NHIS dataset the mean BMI for men with schizophrenia was not noted to differ from that for men without schizophrenia (26.14 vs. 25.63 Kg/m²), whereas women with schizophrenia were significantly more likely to be overweight than women without schizophrenia (27.36 vs. 24.50 Kg/m², $p<0.001$).¹⁴² This trend was consistent across each age decile. The datasets revealed comparable levels of overweight and obesity in men and women with schizophrenia to that seen in the general population.¹⁴² As with schizophrenia, patients with bipolar disorder have been documented to have a higher prevalence of obesity compared to the general population, with prevalence rates of 32 to 35 percent reported, compared to 18 to 22 percent.^{143;311} The risk of being overweight or obese appears to increase with increasing disease severity, and in turn, obesity has been correlated with a poorer outcome in bipolar I

disorder.³¹¹ In particular, increased levels of central adiposity, which is associated with insulin resistance syndrome, has been documented in bipolar patients when compared to the general population.¹⁴⁴ Among bipolar patients, those treated with antipsychotic agents were found to be more obese and to have greater levels of central adiposity than patients who were not.¹⁴⁴

The age-adjusted prevalence rates of overweight and obesity in the general U.S. adult population are 64.5 and 30.5 percent, respectively.²⁷⁸ Patients with schizophrenia appear to be at least as overweight, if not more overweight, than the general U.S. population, and, therefore, have the same, if not a higher risk of developing type 2 diabetes based on weight patterns alone.

1.9.7.4.2 Diet and Physical Activity Level

In community studies, patients with schizophrenia have been documented to exercise less than their non-schizophrenia counterparts.^{309;310} This contrast is heightened among those patients that are hospitalized or institutionalized, with typically lower levels of physical activity documented in these patients. Exercise is important in the pathogenesis of diabetes, not just because of its role in preventing overweight and obesity, but also in terms of its ability to lower levels of insulin resistance.³⁰⁸ The sedative and fatiguing effects of the antipsychotic agents may contribute to reduced physical activity in patients with serious mental illness.³¹ Compared to the general population, patients with schizophrenia have also been noted to have diets that are lower in fiber and higher in saturated fats.^{309;310} This increases their risk of certain disease states such as dyslipidemia, cardiovascular disease, breast, colorectal and prostate cancers contributing perhaps to the excess mortality in this cohort.²⁷⁹

1.9.7.4.3 Cigarette Smoking

An additional mechanism for the comorbidity of schizophrenia and diabetes may relate to cigarette smoking. The prevalence of smoking and

nicotine dependence among patients with schizophrenia is much higher than in the general population at 50 to 90 percent compared to approximately 25 percent.³¹² It has been suggested in two prospective longitudinal studies that among people who smoke 25 cigarettes a day or more, there is an increased risk of developing diabetes compared to non-smokers after controlling for multiple risk factors, with relative risks of 1.42 (95% CI: 1.18-1.72) and 1.94 (95% CI: 1.25-3.03) reported for women and men, respectively.²⁸⁵

In summary, diabetes appears to be more prevalent among patients with schizophrenia and affective disorders than in the general population. While the second-generation antipsychotics have been implicated in this process, additional mechanisms for the comorbidity appear to exist. These include: a genetic predisposition; a diabetogenic lifestyle; as a result of other psychotropic medications or due to biochemical disturbances including hypercortisolemia.¹⁸

1.9.7.5 Diagnosis and Management of Diabetes in Patients with Serious Mental Illness

The diagnosis of diabetes in patients with comorbid mental disorders may be complicated by a number of factors. Symptoms of hyperglycemia may be mistakenly attributed to adverse effects of the antipsychotic medications and other central nervous system agents. For example: polyphagia; polydypsia (dry mouth with a number of medications, or psychogenic polydypsia which has an estimated prevalence of 11 to 42 percent in severe schizophrenia⁵²); blurred vision and fatigue.³¹ Despite frequent contact with primary care and specialist mental health services, patients with mental disorders do not necessarily receive appropriate primary health care.^{313;314} They are less likely to spontaneously report physical symptoms than the general population, and despite high rates of physical illness, these frequently can go undetected.^{313;315} This situation has been

exacerbated by fragmentation of healthcare services and difficulties in obtaining or maintaining healthcare coverage.^{316;317}

1.9.8 Summary

Diabetes is a prevalent condition in the U.S. It is a leading cause of morbidity and mortality and is associated with a substantial healthcare and economic burden. While the second-generation antipsychotic agents are documented to be effective in the management of psychotic and affective disorders and allowing that their use should be encouraged in the absence of superior alternatives, it has been proposed that these agents may precipitate diabetes and are associated with an increased risk of life-threatening hyperglycemic crises. In consideration of the possible predisposition of patients with certain mental disorders to develop diabetes, and the excess morbidity and mortality associated with diabetes in this population, it is imperative to assess the differential risk of diabetes associated with the second-generation antipsychotics so that the safest agent may be used in this vulnerable population.

1.10 Section 8: Use of Second-Generation Antipsychotic Agents

The use of second-generation antipsychotics has increased dramatically in the last decade. As a class, antipsychotic agents accounted for over \$4 billion in retail drug expenditures in the U.S. in 2001, ranking thirteenth in expenditures by drug category.³¹⁸ Ninety-one percent of this expenditure was accounted for by just four agents: clozapine; olanzapine; risperidone and ziprasidone; with olanzapine and risperidone accounting for 45 percent (\$1.8 billion) and 30 percent (\$1.2 billion) of the expenditure, respectively.³¹⁸ Contributing significantly to this expenditure is the high cost of these agents. Whereas the national average price for a prescription was \$49.84 in 2001, the average price for an antipsychotic prescription was \$167.61, with olanzapine the most expensive agent at an average prescription price of \$284.07.³¹⁸ Antipsychotic expenditures account for a considerable percentage of Medicaid prescription expenditure, with psychiatric drugs accounting for approximately 20 percent of the overall cost, 55 percent of which is attributable to antipsychotic drugs.³¹⁹

In the following section, patterns of use of the antipsychotic agents are examined. Of particular interest is the impact of treatment indication on the use of these agents, including the dose prescribed. The influence of a number of demographic variables, including age and ethnicity, are discussed. Additional issues, such as antipsychotic polypharmacy, switch patterns in therapy and medication compliance are examined. This section concludes with a discussion about the potential impact that differences in these variables may have on the occurrence of new-onset diabetes in patients treated with second-generation antipsychotics.

1.10.1 Trends in Prescribing

Using data from the National Ambulatory Medical Care Surveys (NAMCS), antipsychotics were prescribed during 3.2 million office visits in 1989 (0.46% of all visits) compared to 6.9 million visits in 1997 (0.88%), with a total of 35.9 million visits occurring between 1997 and 2000, accounting for nearly 1 percent of all healthcare visits in that period.^{320,321} Non-psychiatric physicians accounted for nearly 30 percent of these prescriptions.³²¹ The use of first-generation antipsychotics has declined as a proportion of all antipsychotic prescriptions in recent years, accounting for 48 percent of antipsychotic prescriptions in 1997 compared to 29 percent of prescriptions in 2000.³²¹ In the NAMCS dataset, the use of second-generation antipsychotics was more prevalent among younger patients.³²¹ Among the second-generation agents, while the mean age of patients treated with olanzapine and risperidone were similar, there were differences in the age distribution, with risperidone used more frequently in patients aged less than 20 years, and in those older than 75 years.³²¹ By comparison, the odds of receiving olanzapine (OR > 1.75) was highest in those aged 35 to 60 years.³²¹ When stratified according to primary diagnosis, and after adjusting for age, race and gender, there was a trend toward the increased use of risperidone compared to olanzapine for non-psychotic conditions such as dementia, depression, attention deficit hyperactivity disorder (ADHD), together with other mental disorders and non-mental disorder conditions, although these differences were not significant.³²¹ In contrast, patients with a diagnosis of psychosis or schizophrenia were significantly more likely to be prescribed olanzapine (OR: 1.62, 95% CI: 1.04-2.52).³²¹

In a report entitled “Care for Veterans with Psychosis in the VHA, FY02”¹⁹ the use of antipsychotic therapy within the National Psychosis Registry for the VA is outlined. (Table 1.11)

Table 1.11: Percentage use of Antipsychotics within the VA Psychosis Registry between 1999 and 2002 for all Patients, and Stratified According to Diagnosis Grouping ¹¹⁹

	1999 %	2000 %	2001 %	2002 %
Among all patients in the registry				
Any antipsychotic ²	56.4	57.0	59.6	59.7
Schizophrenia	73.5	73.3	76.1	77.9
Bipolar Disorder	32.1	35.2	40.8	42.9
Other Psychotic Disorder ³	--	--	--	45.1
Among patients receiving any antipsychotic				
Second-generation antipsychotic	61.7	77.7	80.1	84.9
Schizophrenia	58.7	70.3	77.4	82.0
Bipolar Disorder	69.2	82.0	85.5	89.8
Other Psychotic Disorder ³	--	--	--	88.5

¹ For patients with more than one diagnosis, diagnosis was 'assigned' according to the diagnosis that appeared most frequently in 2002. Ties were resolved using a rank ordering of 1) Schizophrenia; 2) Bipolar Disorder; 3) Other Psychoses.

² First or second-generation antipsychotic.

³ Other psychotic disorders include non-organic psychotic disorders other than schizophrenia, schizoaffective disorder and bipolar disorders.

Note: Registry does not include any usage of depot antipsychotics; therefore, percentage of patients treated with an antipsychotic may be underrepresented between 10 and 20 percent.

The percentage of patients who received treatment with an antipsychotic at any time increased slightly from 56.4 percent in 1999, to 59.7 percent in 2002.¹⁹ When stratified according to diagnosis, patients with schizophrenia were most likely to be treated with an antipsychotic (77.9% in 2002) compared to those with bipolar disorder (42.9%) and those with other psychotic disorders (45.1%).¹⁹ Of note, the psychosis registry does not consistently include use of depot antipsychotic formulations; therefore, these data may under-estimate the use of first-generation antipsychotics in between 10 and 20 percent of patients with schizophrenia.¹⁹ Among those treated with an antipsychotic, the percentage treated with a second-generation antipsychotic increased considerably from 61.7 percent in 1999 to 84.9 percent in 2002, with patients with bipolar disorder most

likely (89.8%) and those with schizophrenia least likely (82.0%) to be receiving second-generation agents.¹⁹ Clozapine was infrequently prescribed and use of this agent was primarily restricted to those with a diagnosis of schizophrenia.¹⁹ Olanzapine and risperidone were the most commonly prescribed agents (38.9 and 37.1%, respectively), although use of quetiapine increased rapidly from 3.2 percent in 1999 to 20.6 percent in 2002.¹⁹ When stratified according to treatment indication, differences in the prescribing rates of these agents were evident, with olanzapine most frequently prescribed to those with a diagnosis of schizophrenia or bipolar disorder, and risperidone use most frequent in those with other psychotic disorders.¹⁹ Regional differences existed in the prescribing rates of these agents, for example the percentage of patients prescribed olanzapine ranged from 29.0 to 51.1 percent.¹⁹ Prescribing trends in North, South and Central Texas (VISN 17) mirrored that of the overall VA population with the exception of higher rates of olanzapine use in VISN 17.¹⁹ (Table 1.12)

Table 1.12: Percentage Use of Second-Generation Antipsychotic Agents within the VA Psychosis Registry in 2002 for all Patients (N=205,620), those within VISN 17¹ (N=8,940), and Stratified According to Diagnosis Grouping²¹⁹

Agent	Overall %		Schizophrenia %		Bipolar Disorder %		Other Psychotic Disorder ³ %	
	All	VISN 17	All	VISN 17	All	VISN 17	All	VISN 17
Clozapine	1.9	2.0	3.0	3.7	0.2	0.2	0.1	0.1
Olanzapine	38.9	44.9	38.4	43.2	44.7	53.0	31.3	37.8
Quetiapine	20.6	19.9	17.9	18.4	26.0	23.2	22.5	19.4
Risperidone	37.1	36.5	36.6	37.7	32.4	29.5	47.6	43.6
Ziprasidone	3.5	3.2	4.0	3.8	2.9	3.2	2.3	1.4

¹ VISN 17 encompasses North, Central, and South Texas together with two counties from Oklahoma (Choctaw and Byran).

² Patients with more that one diagnosis, diagnosis were ‘assigned’ according to the diagnosis that appeared most frequently in 2002. Ties were resolved using a rank ordering of 1) Schizophrenia; 2) Bipolar Disorder; 3) Other psychotic disorder.

³ Other psychoses include non-organic psychotic disorders other then schizophrenia, schizoaffective disorder and bipolar disorder.

Note: Columns may sum to greater than 100% due to potential for dual therapy and antipsychotic switching.

1.10.2 Differences in Prescribing Patterns According to Treatment Indication

As noted in the reports using the National Ambulatory Medical Care Survey (NAMCS) and VA National Psychosis Registry Data, differences exist in the prescribing patterns of the various second-generation antipsychotics.^{19;320;321} With the exception of clozapine, the use of which tends to be limited and restricted to that of the licensed indications, the second-generation antipsychotics are widely used in clinical practice.^{19;320;321} This includes their use for the licensed indications of schizophrenia and bipolar disorder; but also for a wide-range of ‘off-label’ indications.^{19;37-39} In particular, there is a consensus in clinical practice that these agents are indicated in any psychotic disorder where

the term “psychotic disorder” includes: schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; and brief psychotic disorder.⁹⁴ In an expert consensus guideline considering the use of antipsychotics in older patients, it was concluded that antipsychotics were recommended for disorders with psychotic symptoms, i.e., schizophrenia, mania with psychosis, agitated dementia with delusions, psychotic major depression and delusional disorder.¹¹ It was also recommended that the use of antipsychotics was occasionally indicated in mania without psychosis, delirium, and agitated dementia without delusions. However, the experts did not recommend the use of antipsychotics in the following conditions: non-psychotic major depression; generalized anxiety disorder; panic disorder; hypochondriasis; or for irritability, hostility or sleep disturbance in the absence of a major mental disorder.¹¹

As noted earlier, there appears to be a trend toward the increased use of risperidone compared to olanzapine in patients aged less than 18 years, and in those aged 65 years or older, in non-psychotic conditions, and in psychotic conditions other than schizophrenia.^{19;321;322} Supporting this are the results from a large study examining the use of antipsychotics in nursing homes between 1999 and 2000, where 15 percent of patients received treatment with an antipsychotic.¹⁰³ Among those with behavioral and psychological problems associated with cognitive impairment (N=86,514), 18.2 percent received an antipsychotic, of whom approximately 60 percent received a second-generation agent.¹⁰³ A clear difference in the rate of prescribing of the various agents was evident with 66.5 percent of the second-generation antipsychotic use accounted for by risperidone.¹⁰³ Olanzapine was the next most widely used agent (38.2%) with limited use of clozapine and quetiapine noted.¹⁰³ Similar findings were documented in a study using a large national database of psychogeriatric inpatients with dementia disorder from 1996 to 1998, where 36.6 percent of the

patients were receiving antipsychotic therapy, of whom 50.1 percent were treated with risperidone, and 20.9 percent with olanzapine.¹⁰¹

Antipsychotics are widely used in bipolar disorder. In a national study of patients aged 18 years and older admitted to psychiatric inpatient units between 1996 and 2000, 75 percent of patients with bipolar I disorder with psychotic features (74% manic; 78% depressed), and 36 percent of those without psychotic features (33% manic; 41% depressed) were prescribed an antipsychotic.⁶⁵ Of these, approximately two-thirds received a second-generation agent, with olanzapine and risperidone most commonly prescribed.⁶⁵ Lower prescription rates were documented in a study of privately insured patients with bipolar disorder aged 18 to 64 years between 1994 and 1998.⁸⁸ Antipsychotics were used by 24.8 percent of the population, with a total of 16.4 percent of patients using a first-generation agent and 12.4 percent a second-generation agent at any time during the study.⁸⁸ Patients treated with an antipsychotic tended to remain on therapy for a minimum of 12 months.⁸⁸

While only olanzapine is licensed as maintenance therapy (since January 2004) in patients with bipolar disorder, there is considerable evidence that a high percentage of these patients are maintained for long-periods on second-generation antipsychotics. Among patients with psychosis in the VA, patients with bipolar disorder received an average of 6.1 prescription refills in 2002, indicating that many of patients were receiving long-term antipsychotic therapy.¹⁹ In the same cohort, patients with schizophrenia refilled an average of 8.3 antipsychotic prescriptions in 2002, while those with other psychotic disorders refilled an average of 5.3 prescriptions.¹⁹

1.10.3 Dose of Antipsychotic

Independent of age, the dose of antipsychotic recommended in clinical practice is higher for patients with schizophrenia or acute mania with psychosis

than for non-psychotic conditions and conditions such as delirium or dementia with agitation. In the aforementioned expert consensus guideline developed by specialists in the management of older adults, the dose recommended for patients with schizophrenia ranged from 8 to 9.6 percent higher than for acute psychotic mania, and 33 to 59 percent higher than that recommended for patients with delirium or dementia with agitation. (Table 1.13) ¹¹

Table 1.13: Recommended Mean Daily Dose of Second-Generation Antipsychotic Agents (milligrams) in Patients aged 65 Years or Older, Stratified According to Treatment Indication¹¹

Indication	Olanzapine (SD)	Quetiapine (SD)	Risperidone (SD)	Aripiprazole (SD)	Ziprasidone (SD)
Delirium	5.1 (2.2)	84.1 (49.8)	1.2* (0.5)*	13.6 (6.1)	37.8 (15.6)
Dementia with Agitation	6.2** (2.3)	104.2** (54.9)	1.2* (0.7)	11.1 (2.1)	49.3 (33.7)
Schizophrenia	10.6** (3.5)	204.2** (111.9)	2.4 (1.1)*	20.3** (6.4)	79.7 (41.2)
Delusional Disorder	7.7** (3.1)	129.6** (76.7)	1.6* (0.9)	17.9 (7.9)	63.1 (35.0)
Psychotic Major Depressive Disorder	7.0** (3.0)	125.7** (73.8)	1.5* (0.7)	14.2 (4.4)	64.4 (28.0)
Bipolar I Disorder (Psychotic Mania)	9.6* (3.4)	164.4** (101.0)	2.1* (0.9)	19.4 (8.8)	67.2 (31.0)
Bipolar I Disorder (Non-Psychotic Mania)	8.9 (3.4)	147.6 (79.8)	1.9 (1.0)	17.9 (9.1)	57.5 (28.7)

* Preferred Treatment

** Also considered treatment

In a study of patients enrolled in Texas Medicaid, results consistent with these guidelines were found, i.e., doses prescribed to patients with schizophrenia were 40 to 80 percent higher than those prescribed for other indications ($p < 0.001$); and that regardless of mental disorder diagnosis or agent used, the dose prescribed in

patients aged 65 years and older was significantly lower than in patients aged less than 65 years ($p<0.001$).¹²

1.10.3.1 Schizophrenia

The use of an algorithm for schizophrenia was evaluated in a feasibility study by the Texas Medication Algorithm Program (TMAP). The mean maximum daily doses for olanzapine (N=24) and risperidone (N=62) were 14.6 milligrams and 5.7 milligrams, respectively, in 91 inpatients and outpatients with schizophrenia. Overall, dosages were generally considered to be adequate, in that they were within the ranges recommended in the algorithm.³²³ The olanzapine doses were comparable to those in a study of schizophrenia patients enrolled in Michigan Medicaid by Gibson et al., where mean initial daily doses of olanzapine and haloperidol were 9.9 milligrams and 3.8 milligrams, respectively, increasing to 14.2 milligrams and 4.5 milligrams, respectively, three months after treatment initiation.³²⁴ Similarly in a Spanish, open-label prospective study evaluating outpatient use of olanzapine and risperidone in schizophrenia patients, mean initial daily doses were 12.2 milligrams (SD: 4.8mg) and 5.2 milligrams (SD: 2.3mg), respectively, with overall mean daily doses of 13.0 milligrams (SD: 5.0mg) and 5.4 milligrams (SD: 2.5mg), respectively.³²⁵ The dose prescribed correlated with the severity of disease, with significantly higher overall mean daily doses ($p<0.001$) prescribed to those with more severe disease at baseline.³²⁵ Again, comparable results were obtained by Buchanan et al. in the Schizophrenia Patient Outcomes Research Team (PORT) study, where mean daily doses for risperidone were 6.3 milligrams (SD: 2.6mg) for inpatients, and 6.1 milligrams (SD: 2.6mg) for outpatients.³²⁶ Mean daily doses of clozapine reported in this study were 382.8 milligrams (SD: 172.9mg) for inpatients, and 393.9 milligrams (SD: 187.6mg) for outpatients.³²⁶

1.10.3.2 Conditions other than Schizophrenia

As noted, lower doses of antipsychotics are frequently used in other psychotic and non-psychotic conditions compared to schizophrenia. Particular examples include the management of drug-induced psychoses in Parkinson's disease where the use of antipsychotics is generally limited by their propensity to aggravate Parkinsonian symptoms. Clozapine at a dose of 6.25 to 50 milligrams daily and quetiapine 12.5 to 50 milligrams daily have been noted to be efficacious with minimal toxicity.³²⁷ Clearly, these doses are considerably lower than the recommended target daily doses used in schizophrenia (clozapine: 300 to 450 milligrams, and quetiapine 300 to 400 milligrams daily, respectively).^{36;38} In patients with dementia, maintenance doses of antipsychotics that have been recommended include: clozapine 12.5 to 100 milligrams; olanzapine 5 to 10 milligrams; quetiapine 25 to 200 milligrams; and risperidone 0.5 to 2.0 milligrams.¹⁰² These mirror the modal doses observed in a study of 86,514 nursing home residents, 18.2 percent of whom were receiving an antipsychotic.¹⁰³ Modal daily doses were: clozapine 25 milligrams (range 12.5-300mg); olanzapine 5 milligrams (2.5-10mg); quetiapine 50 milligrams (25-400mg) and risperidone 1 milligram (0.5-4mg).¹⁰³ Consistent with the recommendations for the management of psychotic major depressive disorder (Table 1.13), the dose of antipsychotic used in patients with major depressive disorder with and without treatment-resistant depression is lower than that seen in schizophrenia. In a 76-week, open-label study of olanzapine plus fluoxetine in major depressive disorder, the mean modal dose of olanzapine for patients with treatment-resistant depression was 7.7 milligrams (SD=3.9mg), and 7.4 milligrams (SD=3.3mg) for patients with non-treatment-resistant depression.⁹⁸

1.10.4 Age-Related Differences in Prescribing

Antipsychotics are widely used in geriatric patients; however, there are only a limited number of controlled clinical trials that have examined their use agents in this population. Issues regarding the use of antipsychotics in the geriatric population include: excessive use in this population compared to those under the age of 65 years; increased susceptibility to adverse drug reactions due to altered rates of metabolism, polypharmacy with psychotropics and other agents; and increased medical comorbidities.¹¹ As noted earlier, in an expert consensus guideline series considering the use of antipsychotics in patients over the age of 65 years, the dose of antipsychotic recommended was consistently lower than that recommended in non-geriatric populations regardless of the treatment indication.¹¹ (Table 1.13) Of interest, in a similar consensus guideline, developed by national experts in the management of psychotic conditions, but not necessarily specialists in geriatric care, the doses recommended for older adults, while lower than recommended for patients aged less than 65 years, were higher than those recommended by the geriatricians.⁹⁴

1.10.5 Ethnic Differences in Prescribing

A number of studies have highlighted racial disparities in the prescribing of antipsychotic medications. After controlling for other demographic and utilization factors, African-Americans and Hispanic-Americans have been noted to be less likely to receive treatment with second-generation antipsychotics.³²⁸⁻³³² Furthermore, African-Americans have been documented to be more likely to receive treatment with depot therapy and to receive higher doses of first-generation antipsychotics.^{326;331;333} Among the second-generation antipsychotic agents, there are equivocal findings regarding the influence of race on prescribing patterns. Non-white race was associated with a greater likelihood of receiving olanzapine compared to risperidone (OR =1.58, 95% CI: 1.02-2.47) in

one study, whereas no such association was found in another study (African-American: OR: 0.83, 95% CI: 0.69-1.00; Mexican-American: OR 1.00, 95% CI 0.77-1.30).^{321;332} Differential rates of prescribing of antipsychotics by race are an important consideration in any study seeking to examine differences in adverse effects profiles. In particular, it is an important consideration with diabetes, as it is well documented that the incidence and prevalence of diabetes varies by race /ethnicity, with higher rates of diabetes documented among blacks and Hispanics.²⁰¹

1.10.6 Antipsychotic Polypharmacy

Concomitant prescribing of two or more antipsychotics is well described. Estimates of antipsychotic polypharmacy range from 6.8 to 25 percent.^{330;334-337} One study of hospitalized patients in the U.K. described a rate of polypharmacy of 48 percent, although this figure included patients prescribed as required, or PRN medications in addition to a routine antipsychotic.³³⁸ Within the VA, antipsychotic polypharmacy rates have increased annually among all patients registered in the National Psychosis Registry, from 8.7 percent in 1999 to 11.1 percent in 2002.¹⁹ When stratified by diagnosis, antipsychotic polypharmacy was reported in 15.0 percent of patients with schizophrenia, 5.0 percent of those with bipolar disorder and 5.0 percent of those with other psychosis.¹⁹ Combination therapy typically involves a combination of a first- and second-generation antipsychotic (70 to 86%), although combinations of two first-generation agents; two second-generation agents and use of more than two agents have also been described.^{19;336;338;339} The use of dual therapy is considered fifth-line in the management of schizophrenia, to be reserved for use in patients who have failed multiple agents (first or second-generation) when used as monotherapy, in addition to being refractory or only partially responsive to clozapine.³⁴⁰ Little empiric evidence is available to support the efficacy of such combinations and

there is an acknowledged increase in cost and adverse effects.^{338,340} Coprescribing of first- and second-generation agents nullifies the potential benefits of decreased extrapyramidal effects, while maintaining the high cost of therapy, associated with the second-generation agents.³³⁸ It may be difficult to ascertain the extent of true antipsychotic polypharmacy in database studies as patients are frequently cross-tapered when switching from one agent to another.^{334,336} While the necessity of such a process is disputed, gradual withdrawal of clozapine is recommended with the patient gradually discontinued over a three month period.³⁴⁰ Studies have, therefore, used concurrent therapy for 60 days or more as a criterion for antipsychotic polypharmacy.^{19,341}

1.10.7 Switch Rates

A retrospective Dutch study examined the extent of switching antipsychotic therapy in 522 newly admitted patients who commenced antipsychotic therapy.³⁴² Patients commencing treatment with a first-generation antipsychotic were more likely to switch therapy than those commencing a second-generation agent (OR: 1.79, 95% CI: 1.15-2.78), with switch rates of 54.5 percent and 34.4 percent, and median times to switch of 24 days and 170 days reported, respectively.³⁴² Switching to another oral antipsychotic agent is typically described due to inadequate effectiveness or intolerable adverse effects.³⁴² Switches may be within class or inter-class. In the VA National Psychosis Registry, the percentage of patients receiving only one kind of antipsychotic ranged from 70.4 percent for those with schizophrenia, to 78.6 percent for those with other psychoses, with an overall rate of 73.6 percent in 2002.¹⁹ Even after accounting for possible concomitant therapy, it is apparent that switching therapy is not infrequent in this population.¹⁹

1.10.8 Medication Compliance

Medication non-compliance is a major health care problem that impacts the management of all disease states. Estimates of non-compliance range from 30 to 60 percent with higher rates reported in asymptomatic patients.³⁴³ The issue of non-compliance is particularly important in patients with serious mental illness where poor adherence is associated with higher rates of relapse, increased hospitalization rates, increased number of hospital bed days and higher hospital costs.^{341;344;345} Factors that may contribute to non-compliance include: ethnic background; severity of psychotic symptoms; cognitive impairment; comorbid substance abuse; poor insight; financial status; polypharmacy; poor medication tolerability; delayed onset of medication action and delayed time to relapse.^{346;347} Two aspects of medication compliance, adherence and persistence will be considered here, with specific emphasis on compliance with antipsychotic therapy in patients with schizophrenia and bipolar disorder.

1.10.8.1 Adherence to Antipsychotic Therapy

Rates of adherence to antipsychotics range from 11 to 80 percent, with an average rate of adherence of approximately 50 percent.³⁴⁸ In a study using ambulatory pharmacy refill prescription records from a VA database, adherence rates to first- and second-generation antipsychotics were compared. Although not statistically significant, higher rates of adherence were reported with the second-generation agents with rates of 49.9 percent (SD: 33.3%) and 57.4 percent (SD: 33.4%), respectively, reported for first- and second-generation agents at six months ($t=1.97$, $df=286$, $p=0.05$), and 50.1 percent (SD: 30.6%) and 54.9 percent (SD: 26.0%), respectively, reported at 12 months ($t=1.59$, $df=286$, $p=0.11$).³⁴⁸

1.10.8.1.1 Schizophrenia

Adherence to antipsychotic therapy by schizophrenia patients was examined using Medicaid data in a study by Gilmer et al.³⁴⁵ Using a definition of 80 to 110 percent adherence as being adherent, 41 percent of patients were deemed adherent to therapy, with 41 percent categorized as partially, or non-adherent, and 19 percent categorized as excess fillers (that is adherence rates greater than 110 percent).³⁴⁵ Characteristics associated with lower adherence rates included: comorbid substance abuse; younger age; African-American and Latino ethnicity; and living status, with lower adherence in homeless patients and those living independently compared to those living with family or in assisted living facilities.³⁴⁵ When compared to the first-generation antipsychotics (adherence rate 36.9%), similar rates of adherence were found for patients taking second-generation antipsychotics (40.7%, $p=0.13$), with the exception of clozapine (adherence rate: 60.1%, $p<0.001$); and among those taking multiple drugs (34.2%, $p=0.42$).³⁴⁵ Comparable adherence rates were documented in a study using data from the VA National Psychosis Registry.³⁴¹ Among 67,079 patients with schizophrenia or schizoaffective disorder, the mean adherence rate (as measured by medication possession ratio (MPR)) was 0.80 (SD: 0.33) with 60 percent of patients having an adherence rate of 0.80 or higher.^{19;341} Contrary to the findings in other studies, poorer adherence was noted in patients prescribed second-generation compared to first-generation antipsychotics (OR: 1.8, 95% CI: 1.7-1.9).^{341;345;348} Using data from the Schizophrenia Care and Assessment Program (SCAP), significantly higher adherence rates (as measured by MPR) were noted for patients newly initiated on olanzapine (MPR: 0.75) compared to new initiators on risperidone (MPR: 0.69) or quetiapine (MPR: 0.61).³⁴⁹

1.10.8.1.2 Bipolar Disorder

In a prospective, 12-month study of patients with bipolar disorder following hospitalization for a manic or mixed episode, only 47 percent of patients were documented to be fully adherent to therapy (defined as an adherence rate of 75% or greater), with non-adherence (zero to 25% adherence) reported for 26 percent of patients.⁶⁰ The rate of adherence to therapy did not differ between medication regimens that is between: mood stabilizer alone; mood stabilizer plus antipsychotic; mood stabilizer plus antidepressant; antipsychotic alone; or antidepressant alone.⁶⁰ Comorbid substance misuse was predictive of nonadherence and as anticipated, patients that were fully adherent to therapy were more likely to achieve syndromic recovery.⁶⁰ Higher adherence rates were reported in a small study (N=44) where patterns of medication adherence were examined in a structured interview of patients with concurrent bipolar and substance abuse disorders, 31 of whom (70%) were prescribed neuroleptic agents.³⁵⁰ Approximately 65 percent of patients reported being adherent to neuroleptic therapy at least two-thirds of the time, with 13 percent of patients reporting being adherent only one-third of the time.³⁵⁰

1.10.8.2 Persistence with Antipsychotic Therapy

A Canadian population-based cohort study examined persistence with ambulatory therapy in first-time users of the second-generation antipsychotics: clozapine; olanzapine; quetiapine and risperidone.³⁵¹ Persistence rates were highest for patients treated with clozapine without prior use of first-generation antipsychotics (hazard rate (HR) of discontinuation 0.33, 95% CI: 0.26-0.41) and in those treated with olanzapine regardless of prior antipsychotic use (HR: 0.78, 95% CI: 0.74-0.81 (past use); HR: 0.88, 95% CI: 0.85-0.92 (no past use)).³⁵¹ While patients treated with risperidone had lower persistence rates, they were

also less likely to receive concomitant antipsychotic therapy, as well as less likely to have any antipsychotic agent prescribed after discontinuation.³⁵¹

A number of studies have compared persistence rates in patients prescribed first- and second-generation antipsychotics. Contrary to expectations, superior persistence rates were documented with first-generation antipsychotics after eight months of treatment ($\chi^2=5.58$, $df=1$, $p<0.02$) in a study of prescription refill records of 25,000 patients from a national refill chain.³⁵² Among the second-generation agents, persistence with clozapine was significantly higher than with olanzapine (71% vs. 40%, $\chi^2=39.72$, $df=1$, $p<0.001$); quetiapine (33%, $\chi^2=46.98$, $df=1$, $p<0.001$); and risperidone (40%, $\chi^2=41.37$, $df=1$, $p<0.001$).³⁵² Zhu et al. documented longer rates of persistence with olanzapine (259 days) than with risperidone (237 days) or quetiapine (212 days) in a study using data from the Schizophrenia Care and Assessment Program (SCAP).³⁴⁹ When examined independently of the gap between prescriptions, patients treated with olanzapine had the lowest treatment discontinuation rate, and those treated with quetiapine the highest.³⁴⁹ Similar findings were documented in a study by Opolka et al. using data from Texas Medicaid with olanzapine associated with significantly longer persistence rates ($p<0.001$) than risperidone or haloperidol.³⁴⁷

1.10.8.3 Summary

In summary, non-compliance with medications is prevalent in patients receiving antipsychotic therapy regardless of the indication for treatment. While superior compliance would be anticipated with second-generation compared to first-generation antipsychotics based on improved tolerability, results from such comparisons have been equivocal. Among the second-generation antipsychotics, superior adherence and persistence rates have been documented with clozapine and olanzapine.

1.10.9 Potential Impact of Prescribing Trends on the Occurrence of Antipsychotic-Induced New-Onset Diabetes

While glucose dysregulation appears to be associated with the use of second-generation antipsychotics, it is difficult to ascertain the extent of the problem. Differential patterns and rates of prescribing of antipsychotics may influence the findings of any study that seeks to examine this adverse effect. Important considerations include the impact of dose and treatment indication. It has been noted that there is a higher prevalence of diabetes in patients with schizophrenia and bipolar disorder than in the general population, which is independent of antipsychotic use.^{13-15;17;18;291} Cohort studies indicate that patients with conditions other than schizophrenia tend to be treated with lower doses of antipsychotics than those with schizophrenia.^{12;103}

Studies with a preponderance of older patients may include disproportionate numbers with dementia and other psychotic disorders. The use of lower treatment doses in this population may limit the potential to detect a dose-related effect, should one exist. However, it may not be sufficient to control for age differences alone, as it has been shown that independent of age, patients with schizophrenia are treated with higher doses than those with other psychotic and non-psychotic conditions.^{11;12} This, combined with the fact that older patients may lack the diathesis for developing diabetes, may skew study findings particularly if the various second-generation antipsychotics are prescribed at different rates in this population.

Differential rates of prescribing of antipsychotics by race are also an important consideration in any study seeking to examine differences in adverse effects profiles. In particular, it is an important consideration with diabetes, given the well documented genetic predisposition of certain racial/ethnic groups for diabetes.²⁰¹

Finally, in any study examining treatment-related adverse effects, the level of treatment exposure is an important consideration. Differential rates of medication compliance between the various antipsychotic agents may bias findings, and as such compliance represents an important control variable.

1.11 Section 9: The Use of Large Databases in Health Outcomes Research

1.11 1 Introduction

While randomized controlled trials are historically the gold standard in objective research, they are expensive and time-consuming to conduct.^{215;353;354} In addition, they have a number of limitations which reduce their external validity or generalizability.^{215;353;354} Specifically, randomized controlled trials tend to have strict inclusion and exclusion criteria, are frequently conducted in specialized clinical settings, are often short-term in nature, and may have an added limitation of the Hawthorne effect.^{353;354} Claims databases are increasingly being used to provide answers to healthcare questions.³⁵³ Although developed for the purpose of claims processing and tracking, these databases are increasingly being adapted to facilitate both retrospective and prospective analyses.³⁵³

In this study, data from a large claims database, Texas Medicaid were used. This section will proceed with a brief overview of the advantages and limitations of using claims databases, with specific reference to the use of the Medicaid database for health care research.

1.11.2 Advantages

Key advantages of claims database research are the size and ease of access of many of these databases. As these databases are not custom-generated for the purpose of research, they tend to be less costly than clinical trials.³⁵³ Due to the large size of many of these databases, they facilitate longitudinal research of healthcare utilization by large cohorts of patients, providing considerable statistical power at low cost.^{215;353} In epidemiological studies, these databases are realistically the only feasible means for studying risk factors for rare diseases and the occurrence of rare adverse events.²¹⁵ By virtue of the fact that these databases

reflect ‘real life’ healthcare and are not limited by strict inclusion entry criteria, they include subjects that are more representative of the population to whom the results will be applied.³⁵⁴ Due to their retrospective nature, these databases allow for flexible methodological study designs that are non-intrusive and inherently free of recall or interviewer bias.³⁵³

Support for the validity of observational studies comes from a number of sources. In a study published in the New England Journal of Medicine in 2000 that included studies reported between 1985 and 1988, the results from observational studies and randomized clinical trials were compared.³⁵⁵ Little evidence of systematic bias with observational studies was found, and the authors concluded that there was no evidence that these studies provided estimates of treatment effects that were either consistently larger, or qualitatively different than those obtained in randomized clinical trials.³⁵⁵ Comparable findings have been documented in a number of similar studies.^{354;356}

1.11.3 Limitations

As noted, claims databases are usually not custom-generated for the purpose of research and thus represent secondary data sources. A key disadvantage to their use is, therefore, that they may not contain information on variables of interest to the researcher. Claims database research may have a number of limitations which impact on the validity of study results. For the purpose of clarity, these limitations will be discussed in terms of threats to specific types of study validity: construct validity; internal validity; and external validity. The relevance of these threats to this study proposal, and mechanisms of dealing with these threats will be discussed in detail.

1.11.3.1 Construct Validity

This refers to the degree to which an instrument or variable measures the underlying trait or phenomenon that it claims to measure. In this study, the dependent variable of interest was the occurrence of new-onset diabetes. This was detected by an ICD-9 code of 250.xx for diabetes, or a prescription for insulin, an oral hypoglycemic agent or an insulin sensitizing agent. As noted previously in Table 1.9, the medications to treat diabetes are disease-specific for diabetes, with limited off-label use for other conditions. New indications and off-label use of these medications for conditions such as for insulin-resistance syndrome and the prevention of diabetes is expanding; however, the literature supporting such use is relatively new. Off-label use of these agents in the timeframe of this study was, therefore, thought to be negligible and the use of these medications as a proxy for a diabetes diagnosis is a reasonable assumption.

1.11.3.2 Internal Validity

Internal validity has been defined as “the degree to which it can be inferred that the experimental treatment (independent variable), rather than uncontrolled extraneous factors, is responsible for observed effects.”³⁵⁷ That is, the extent to which we are making appropriate inferences about the relationships between study variables. With regard to database research, a number of threats to internal validity have been identified as being particularly important. These include: validity of diagnostic information; exposure misclassification; and problems with confounding, including channeling bias. A brief discussion of these threats with reference to the Medicaid database will follow.

1.11.3.2.1 Diagnostic Information

The successful use of databases in studies is dependent on the accuracy of the information contained therein. The ICD-9 patient diagnostic coding system is

frequently used in claims based research to identify populations of interest.³⁵³ The reliability and validity of this coding have been disputed, and found to vary by disease state.³⁵³ In a study that attempted to verify the accuracy of schizophrenia diagnoses among Medicaid patients, psychiatrists classified 86.8 percent of patients with a treatment claim for schizophrenia as definitely (78.3%) or probably (8.5%) having schizophrenia.³⁵⁸ In contrast, among patients with claims for chronic mental illness other than schizophrenia, 27.5 percent (N=43) were classified as definitely or probably having schizophrenia.³⁵⁸ The authors concluded that most diagnoses of schizophrenia in the Medicaid claims database are accurate, but that claims data may underestimate the true number of affected patients.³⁵⁸

Complicating the picture of accuracy of diagnoses within a database is the inherent difficulty in differentiating between a number of disease states, including between schizophrenia and bipolar disorder. While considered to be separate entities with distinguishing clinical characteristics, differentiating between these disorders may be complicated by factors such as: changes in the manifestation of the disease over time; changes in the course or appearance of the disorder due to comorbid diseases including substance abuse; demographic variables that alter the symptoms, course or perception of the illness; and the fact that there appears to be a shared genetic link between the disorders.^{359;360}

In a study using data from a non-VA public inpatient psychiatric hospital that examined the stability of diagnosis in bipolar disorder, 28.5 percent (N=68) of patients with an initial diagnosis of bipolar disorder had a change of diagnosis within a seven-year period.³⁵⁹ Of these, 70.6 percent (N=48) were subsequently identified as having schizophrenia.³⁵⁹ Similarly, among 701 patients with an initial diagnosis other than bipolar disorder, 16.1 percent (N=113) were subsequently identified as having bipolar disorder, of whom 24.8 percent (N=28)

had an initial diagnosis of schizophrenia.³⁵⁹ Factors that were significantly associated with a diagnostic change from bipolar disorder included: male gender; African-American ethnicity and comorbid substance abuse.³⁵⁹ Similar findings were documented in a study by the same authors investigating the stability of diagnosis in schizophrenia.³⁶¹ Of 256 patients with an initial diagnosis of schizophrenia, 21.9 percent received a different diagnosis during a subsequent hospitalization, and 32.8 percent of 680 patients with an initial diagnosis other than schizophrenia were subsequently diagnosed as having schizophrenia.³⁶¹

Good reliability of the VA administrative files was demonstrated in a 1995 study that compared details from administrative files and patient medical records.³⁶² In particular, there was good agreement between the files for the demographic variables of gender and ethnicity (kappa (κ): 0.897–0.978), for principal diagnoses for inpatient discharges (e.g., schizophrenia, κ : 1.000; affective psychoses, κ : 0.794; diabetes, κ : 0.795); and for secondary diagnoses for inpatient discharges (e.g., diabetes, κ : 0.823).³⁶² The authors did note that using the administrative files may overestimate the prevalence of specific medical conditions compared to patient medical records, including: a significant overestimation of the prevalence of diabetes by 19.1 percent ($p=0.003$); and a non-significant overestimation of the prevalence of schizophrenia by 8.0 percent ($p=0.318$).³⁶² Among patients with psychoses enrolled within the VA in 2001 and 2002, 94.5 percent of patients with schizophrenia had the same diagnosis in both years while 93.7 percent of those with bipolar disorder, and 81.6 percent of those with a diagnosis of other psychoses maintained the same diagnosis in both years.¹⁹

Based on these findings, it appears that longitudinal follow-up is necessary in order to validate diagnoses in database studies. Database studies have used a variety of techniques to counteract diagnostic instability including

using the modal diagnosis (based on ICD-9 medical code) as the primary diagnosis, and using a hierarchical taxonomy where the patient is classified according to mutually exclusive diagnostic categories of: schizophrenia; bipolar disorder; other psychotic /delusional disorder; and other mental health diagnoses.¹⁹

1.11.3.2.2 Exposure Misclassification

With claims database research, it is rarely possible to verify patient exposure or non-exposure to a treatment. In the absence of a superior method, drug exposure is typically inferred from prescription redemption records.³⁶³ This may over- or under-estimate exposure in that patients may not take prescriptions that they fill, or alternatively obtain prescription medications from sources other than that recorded. There is good consensus that automated pharmacy claims are one of the best sources of information on drug utilization.³⁶³ The primary issue then is patient compliance and use of drugs from other sources. Antipsychotic medications are all prescription-only medications, which limits the potential to source them from alternate routes. There is a potential for exposure misclassification with injectable antipsychotic preparations which are not uniformly recorded in pharmacy claims databases, and this will be a limitation of this study.^{19;363} By incorporating patient adherence and persistence with treatment as control variables, the potential for bias as a result of exposure misclassification can be minimized.

As noted, a further source of exposure bias relates to the potential for patients to obtain services from alternate systems other than Medicaid. It is counterintuitive that patients enrolled in Medicaid who maintain eligibility of coverage, would obtain medical care, in particular prescription medications, from elsewhere given that these medications are available free of charge to them from Medicaid. An exception would be in states, including Texas, that impose a three-

prescription maximum per month cap, with the potential that patients have out-of-pocket expenditure for medications and that these are then omitted from the database. The potential for misclassification bias is, therefore, a limitation associated with the Medicaid database. In that it is limited in nature, and unlikely to systematically differ between the antipsychotic agents, it is unlikely to interfere significantly with the inferences drawn from the study.

1.11.3.2.3 Confounding

Confounding has been defined as “differences between the study cohorts that may affect treatment outcome.”³⁵³ Typically, it is addressed through statistical techniques. Inherent in this method however is the assumption that the researcher is aware of, or has access to all the variables that may confound the results. In a study of new-onset diabetes this would include controlling for known risk factors for diabetes such as age, race, family history, lifestyle, BMI, and a history of hypertension, dyslipidemia, gestation diabetes, or IGT.²²⁴ In the absence of this information, the statistical adjustment may be incomplete, thereby threatening the validity of the study findings. One particular form of confounding, “confounding by indication” or channeling bias, will be discussed in detail now.

1.11.3.2.3.1 Channeling Bias

This has also been referred to as “confounding by indication,” and occurs when a potential association between a drug and disease is altered by disease severity.³⁶⁴ For example, based on information from case reports, adverse drug surveillance systems and cohort studies, an expert panel has recommended that the use of clozapine and olanzapine should be avoided if possible in patients with multiple risk factors for diabetes.²⁶¹ Instead, they recommend that the patients be treated preferentially with aripiprazole or ziprasidone, two agents not associated with significant weight gain or diabetes to date.²⁶¹ An increase in the number of

cases of diabetes in patients treated with these agents may, therefore, inappropriately be inferred to be due to these “low risk” agents, rather than due to an inherently higher risk of diabetes in the baseline population. Equally, channeling only patients with a perceived low risk of diabetes onto olanzapine therapy may lead to an apparent lower risk of diabetes in olanzapine users. As the data for this study are from 1997 to 2001, they pre-date both the recommendations from the expert committee in 2004 and the retrospective case-control and cohort studies published in December 2001 to 2004.^{3;4;9;10;228;230-232;235-238;241;243;246;250;261} Therefore, this particular form of channeling bias is an unlikely confounder in this study.

A further potential source of channeling bias is the differential rates and extent of prescribing of antipsychotics according to mental health diagnosis. It has been noted that both schizophrenia and bipolar disorder are associated with a higher prevalence of diabetes than in the general population.^{13-15;17;291} If the profile of antipsychotic prescribing differs in these patients compared to, for example the profile of prescribing in patients with other psychotic conditions which have not been associated with an increased risk of diabetes, then there is the potential that differences in the incidence of diabetes would be inappropriately assumed to be due to differences in risk associated with the various agents as opposed to differences in baseline population risk. While of major concern, this effect could be controlled for by stratifying patients according to treatment indication and dose of antipsychotic.

1.11.3.3 External Validity

This refers to study generalizability, that is, the extent to which inferences from the study results may be generalized to other study populations.³⁵³ A key feature is, therefore, the characteristics of the proposed study population and the extent to which it is representative of the overall U.S. population. Eligibility for

Medicaid, which was created in 1965 as a health insurance system to provide access to medical care for indigent and disabled, is determined at a state level; however, there are certain groups for which mandatory coverage is required in order for the program to maintain federal funding.³⁶³ Because of these requirements, the enrolled Medicaid population may differ from year to year, and from state to state.³⁶³ Furthermore, it is systematically different from the general population in the U.S., being characterized by an over-representation of children, females and nonwhites.³⁶³ While problematic for many population based studies, the use of the Medicaid database to study patients with serious mental illness is reasonable. Specifically, in the area of schizophrenia, public funding has been reported to account for 81 percent of health care needs of this population. In a study of ambulatory care patients with serious mental illness, 52.4 percent of patients had Medicaid coverage, 46.4 percent Medicare coverage, and 20.8 percent of patients were dual-eligible.³⁶⁵ A further 5.3 percent of this group was in receipt of veteran's benefits, while 9.4 percent were uninsured and 9.1 percent had private insurance.³⁶⁵ A higher percentage of patients with schizophrenia were reported to be uninsured or privately insured in a study using data from the National Comorbidity Study, with 25.3 percent uninsured, 43.6 percent privately insured and 31.3 percent insured by public sources (primarily Medicaid and Medicare).³⁶⁶ However, these patients did not necessarily meet the criteria for 'seriously mentally ill', and while based also on an ambulatory population, included only those with residences.³⁶⁶ Using either sample, 30 to 50 percent of patients were in receipt of Medicaid coverage; therefore, a study using this claims database is representative of a high percentage of patients with schizophrenia. Other issues that may reduce the external validity of a study include differences in regional prescribing practices, formularies, and co-payment structures, all of which may limit the generalizability of the study.³⁵³

1.11.4 Summary

The use of claims databases in outcomes research is common. These databases allow for cost-efficient and timely retrieval of information and have the advantage of good external validity or generalizability. There are a number of important considerations in the use of these databases, particularly in relation to the internal validity of the proposed study. Careful study design, accompanied by an acknowledgment and correction for limitations where possible, allows high-quality and useful information to be derived in an efficient manner. The use of the Medicaid claims database was discussed briefly with regard to this study. Possible limitations in using this dataset and their implication for study validity were highlighted.

1.12 Section 10: Study Rationale, Objectives and Hypotheses

1.12.1 Study Rationale

In September 2003, the Center for Drug Evaluation and Research (CDER) requested that the labeling for second-generation antipsychotic agents be changed to acknowledge the perceived association between the use of these agents and the development of hyperglycemia.²⁰ In requesting this change, the CDER acknowledged the limitations of the available data. Although there are multiple case reports, there is a dearth of well-controlled trials. Many of the studies conducted were limited by small sample sizes, absence of control groups, and an inability to confirm fasting blood glucose levels. Cohort studies have used varied eligibility criteria and methodologies with the result that the findings are conflicting. To date, there is insufficient evidence to determine the differential propensities of the various second-generation agents to cause diabetes. The CDER highlighted the need for additional research to assess this relative risk and to identify patient sub-groups that may be more susceptible to this adverse event.

This study had two overall goals. The primary goal was to determine the relative risk of new-onset diabetes associated with the different second-generation antipsychotic agents. Secondary goals included profiling the characteristics of patients taking second-generation agents within the Medicaid database, and profiling the antipsychotic prescriptions for these patients. The primary goal of the study (ascertaining relative risk) aimed to facilitate clinicians in assessing the implication of using the different antipsychotics in Medicaid patients. The secondary goals (profiling patients and prescriptions) aimed to allow these decision-makers gain better insight into the characteristics of patients receiving antipsychotic treatment, and the manner in which these patients are treated. This study aimed to identify susceptible sub-groups so that antipsychotic

treatment could be more precisely tailored to patient need while considering the potential hazards associated with such treatment.

The study was comprised of three phases. In phase I, the Texas Medicaid study population was described with regard to demographic variables and antipsychotic utilization patterns. Phase II of the study measured the prevalence of diabetes in the study population. Finally, phase III of the study examined the incidence of diabetes in the study population.

1.12.2 Objectives and Hypotheses

The following objectives were the focus of this study. Please note that the analyses conducted depended on the extent and quality of the available data. All hypotheses relating to these objectives were tested in the null.

1.12.2.1 Phase I: Epidemiology and Antipsychotic Utilization Patterns

1.12.2.1.1 Objective 1

To profile the demographic and clinical characteristics of the Texas Medicaid study population. The demographic characteristics available from patient medical records were age, gender and race/ethnicity. Clinical characteristics with the potential to confound the relationship between exposure to an antipsychotic and the development of diabetes were examined. These included: mental health diagnoses, dyslipidemia and hypertension.

1.12.2.1.2 Objective 2

To examine antipsychotic utilization patterns in the Texas Medicaid study population. Of interest were variations in treatment patterns that may confound the relationship between antipsychotic exposure and the development of diabetes. These included differences in prescribing rates of the different agents, differences in treatment doses and differences in patient compliance.

- H_0 (1a-d) The percentage of patients receiving treatment with the different antipsychotic agents (first-generation agents, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) will not differ significantly when stratified according to patient age $H_{0(1a)}$; gender $H_{0(1b)}$; race/ethnicity $H_{0(1c)}$; or primary mental health diagnosis $H_{0(1d)}$.
- H_0 (2a) The classification of mean daily antipsychotic dose as ‘Low,’ ‘Medium,’ or ‘High’ will not differ when stratified according to the second-generation antipsychotic agent (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) used.
- H_0 (2b-f) The mean daily dose for the second-generation antipsychotics clozapine $H_{0(2b)}$, olanzapine $H_{0(2c)}$, quetiapine $H_{0(2d)}$, risperidone $H_{0(2e)}$, and ziprasidone $H_{0(2f)}$ will not differ significantly when stratified according to patient age.
- H_0 (2g-k) The mean daily antipsychotic dose for the second-generation antipsychotics clozapine $H_{0(2g)}$, olanzapine $H_{0(2h)}$, quetiapine $H_{0(2i)}$, risperidone $H_{0(2j)}$, and ziprasidone $H_{0(2k)}$ will not differ significantly when stratified according to the primary mental health diagnosis.
- H_0 (3a-j) Adherence and persistence with the second-generation antipsychotic agents will not differ significantly when stratified according to patient age $H_{0(3a-b)}$; gender $H_{0(3c-d)}$; race/ethnicity $H_{0(3e-f)}$; primary mental disorder diagnosis $H_{0(3g-h)}$; or type of agent $H_{0(3i-j)}$.

1.12.2.2 Phase II: Evaluation of the Prevalence of Diabetes

1.12.2.2.1 Objective 3

To examine the prevalence of diabetes mellitus in patients enrolled in the Texas Medicaid study population according to the primary mental health diagnosis after controlling for demographic (age, gender, race/ethnicity), clinical (i.e., hypertension, dyslipidemia) and medication (use of concomitant diabetogenic medications) risk factors for diabetes.

$H_0(4a)$ The prevalence of diabetes will not differ significantly when stratified according to the primary mental disorder diagnosis after controlling for demographic, clinical and medication risk factors for diabetes.

1.12.2.3 Phase III: Evaluation of the Incidence of Diabetes

1.12.2.3.1 Objective 4

To examine the incidence of diabetes in patients enrolled in the Texas Medicaid study population according to the class of antipsychotic and according to the type, dose and treatment indication for the second-generation antipsychotics after controlling for demographic (i.e., age, gender, race/ethnicity) clinical (i.e., hypertension, dyslipidemia, primary mental disorder diagnosis) and medication (i.e., antipsychotic therapy compliance, mean daily dose, use of concomitant diabetogenic medications for diabetes) risk factors for diabetes.

$H_0(5a-b)$ The time to occurrence of diabetes will not differ significantly when stratified according to the class of antipsychotic agent $H_{0(5a)}$, or specific type of second-generation agent $H_{0(5b)}$ after controlling for demographic, clinical and medication risk factors for diabetes.

- H₀(6a-b) The incidence of diabetes will not differ significantly when stratified according to the class of antipsychotic agent H₀(6a), or specific type of second-generation agent H₀(6b) after controlling for demographic, clinical and medication risk factors for diabetes.
- H₀(7a-e) The incidence of diabetes will not differ significantly according to the dose of the second-generation antipsychotic agents: clozapine H₀(7a); olanzapine H₀(7b); quetiapine H₀(7c); risperidone H₀(7d); or ziprasidone H₀(7e); after controlling for demographic, clinical and medication risk factors for diabetes.
- H₀(8a-e) The incidence of diabetes will not differ significantly when stratified according to the primary mental disorder diagnosis for the second-generation antipsychotic agents: clozapine H₀(8a); olanzapine H₀(8b); quetiapine H₀(8c); risperidone H₀(8d); or ziprasidone H₀(8e); after controlling for demographic, clinical and medication risk factors for diabetes.

Chapter 2: Methodology

2.1 Chapter Overview

This chapter describes the methods used to evaluate the association between second-generation antipsychotic use and diabetes. The study design is described including details of the data source, the study population and the timeframe of the study. A detailed presentation of the study variables and how they were operationalized follows. The chapter concludes with a description of the data collection methods, the estimated sample size required for the study and a discussion of the statistical analyses employed for each of the specific study objectives.

2.2 Institutional Review Board Approval

This study was approved by the institutional review boards (IRB) of The University of Texas at Austin and Texas Medicaid. A waiver of informed consent was obtained from the relevant review boards as the research contained no more than minimal risk to the research subjects, the waiver did not affect the rights and welfare of the subjects, and the research could not reasonably have been conducted without the waiver. In accordance with the IRB requirements of the relevant institutions, only de-identified data were collected to ensure confidentiality of patient information.

2.3 Study Design

This was a retrospective analysis using demographic, prescription and medical records for adults aged 18 years or older enrolled in Texas Medicaid who received at least one antipsychotic prescription (first or second-generation) between 1997 and 2001 (see section 2.3.3).

This study encompassed three phases. In phase I, the study population was described with regard to demographic variables and antipsychotic utilization patterns. In phase II, the prevalence of diabetes was examined. Finally, phase III of the study examined the incidence of diabetes in the population.

2.3.1 Data Source

Data were derived from Medicaid, as represented by Texas Medicaid, a brief background of which is included here.

2.3.1.1 Medicaid

The Medicaid program, which was established in 1965, is the largest single source of health insurance in the U.S. Eligibility for this program is based on financial and categorical eligibility requirements and is determined at a state level; however, there are certain groups for which mandatory coverage is required in order for the programs to maintain federal funding.³⁶⁷ Because of these requirements, the Medicaid population is systematically different from the general population in the U.S., being characterized by an over-representation of children, females and nonwhites.³⁶⁷

Medicaid provided health insurance or long-term care services to nearly 10 percent of Texans in 2002, with an average monthly enrollment of 2.10 million beneficiaries. The majority of these beneficiaries were non-disabled children (59%). The remainder of the population was comprised of blind and disabled (11%), aged (9%), adults (16%) and others (5%, primarily those receiving long-term care). The population was primarily female (56%), non-white (74%) and young, with 64 percent of beneficiaries under the age of 21 years. Hispanics (51%) and African Americans (19%) represented the largest minority populations. Of note however, Caucasians comprised 42 percent of the population over the age of 65 years. Services provided by Medicaid include:

basic health services such as physician services; inpatient and outpatient hospital services; long-term care; pharmacy; and lab and x-ray services. Of note, adult hospitalization in a free-standing psychiatric hospital is not reimbursed in the fee-for-service Medicaid program. The state currently limits the number of prescriptions covered under the program to a maximum of three prescriptions per month, each with a maximum of 120 days supply. This restriction does not however apply to children, those in nursing homes or those enrolled in Medicaid managed care plans. In 2003, Texas Medicaid paid in excess of \$1.9 billion for over 34 million prescriptions.³⁶⁷

In 2003, over 95,000 Texas Medicaid enrollees had a diagnosis of diabetes with diabetes-related expenditures estimated to be over \$400 million for that year.³⁶⁸ In an earlier report from 2002, the majority of patients with a diagnosis of diabetes were aged 18 years or older (93.7%), with patients aged 45 to 64 years representing the largest cohort (54.2%). (Data on file, Texas Health and Human Services Commission (THHSC), obtained 10/15/2004) Assuming these percentages did not change between 2002 and 2003, it can be estimated that approximately 89,000 adults had a diagnosis of diabetes in 2002, giving a prevalence of 10.7 percent among adults enrolled in Texas Medicaid that year. The majority of Texas Medicaid patients with diabetes are Hispanic (47.3%), with Blacks accounting for 24.7 percent, and Whites 22.2 percent of this cohort. (Data on file, THHSC, obtained 10/15/2004)

Mental disorders are also prevalent among Medicaid enrollees. The Medicaid program accounts for over one-third of all public health spending and one-fifth of all spending on mental health and substance abuse treatment.³⁶⁹ In a study of ten state Medicaid programs, Buck et al. examined the use of mental health and substance abuse services by Medicaid enrollees under the age of 65 years who were not dual-eligible for Medicare.³⁷⁰ Users of these services

comprised seven to 13 percent of the study population, the majority of whom received only mental health services (86.4%).³⁷⁰ The expenditure on these services accounted for 11 percent of the total Medicaid budget in those states.³⁷⁰ When all healthcare expenditures for users of mental health and substance abuse services were included, this figure increased to 28 percent of the state budgets.³⁷⁰ Use of these services increased with enrollee age, with over 15 percent of the population aged 21 to 44 years, and 20 percent of the population aged 45 to 64 years receiving mental health and substance abuse services.³⁷⁰

2.3.2 Study Population

Patient level data were collected according to strict inclusion / exclusion criteria as detailed below.

2.3.2.1 Inclusion / Exclusion Criteria

To be eligible for inclusion in the study, patients were required to meet the following criteria: 1) age 18 years or older; 2) receiving a first or second-generation antipsychotic agent, but having a six-month (180-day) antipsychotic-free window prior to the identification of the index prescription; 3) continuous enrollment for six months (180 days) prior to, and 12 months (365 days) subsequent to the index date; with 4) evidence of at least one medical claim in that period. The study was limited to those receiving antipsychotic monotherapy. For phase III of the study, examining the incidence of diabetes, patients had to meet an additional criterion, that is, no history of diabetes in the 180 days prior to study enrollment.

All antipsychotic dosage forms (oral, liquid, short-acting injectable and depot formulations) were included in the data set. No limits on the duration of antipsychotic treatment were set. No data were collected on the second-generation antipsychotic aripiprazole (Abilify®) as this product was not licensed

by the FDA until after the study period. Data relating to another agent, ziprasidone (Geodon®) were limited, as this product was licensed in February 2001.

Patients were followed for a maximum of 365 days from the index date, or until an endpoint occurred, where an endpoint was defined as: occurrence of diabetes; switching of antipsychotic therapy (including commencing dual antipsychotic therapy); discontinuation of the antipsychotic agent (with the patient observed for an additional 30 days lag-time for the occurrence of diabetes); or the end of follow-up data. Patients could be enrolled in the study on one occasion only.

As noted, to ensure the completeness of the service and prescription data, subjects were required to have continuous enrollment in the program, with evidence of at least one medical claim, during the 180 days prior to, or the 365 days subsequent to the index prescription date.

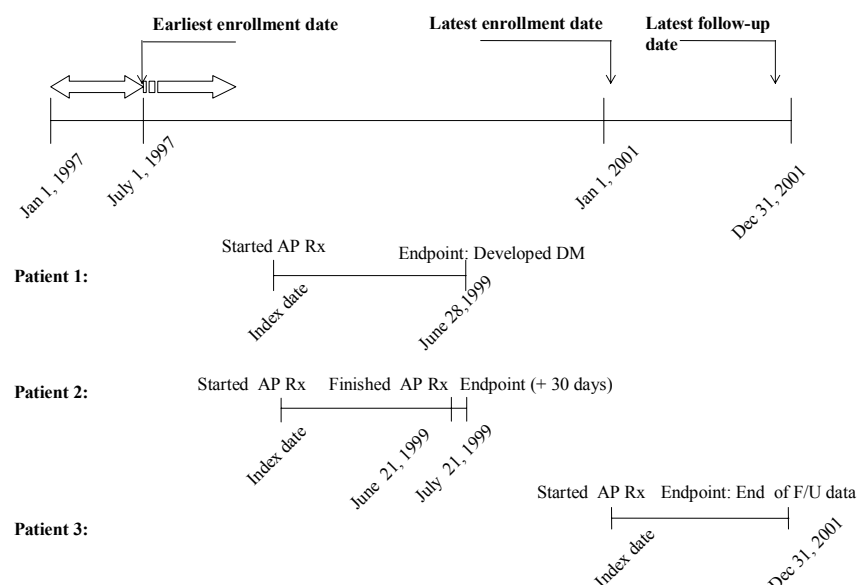
2.3.3 Timeframe

The overall timeframe of this study was a five-year period from January 1, 1997 to December 31, 2001. As discussed in Chapter 1 (section eight), this period was selected to minimize the risk of channeling bias, as it predated the publication of studies on the association between antipsychotic use and diabetes and also the recommendations of an expert panel regarding the choice of antipsychotics for patients at risk of diabetes.^{3;4;9;10;222;227;228;230-232;235-238;241;243;246;250;277} As previously outlined, to be eligible for the study, patients were required to have six months of continuous enrollment prior to the index date and a minimum of 12 months follow-up data. Therefore, while the maximum observation period for the study was five years, patients could only be enrolled in the study between July 1, 1997 and January 1, 2001. The duration of follow-up

varied by patient as patients could enter or exit the study at different times. The latest possible date of follow-up was December 31, 2001.

A schematic illustration of the study timeline with patient examples is outlined in Figure 2.1.

Figure 2.1: Study Timeline and Patient Examples



2.3.4 Study Phases

This study included three phases. Phase I described the study population with regard to demographic variables and antipsychotic utilization patterns. Phase II examined the prevalence of diabetes in the population. Finally, phase III of the study examined the incidence of diabetes in the population. Eligibility for the study was determined by the inclusion and exclusion criteria outlined above, with as noted, the additional restriction for phase III of the study that participants not have diabetes at the time of study enrollment, or in the preceding six months.

2.4 Study Variables

In the following section, an operational definition is provided for each of the dependent and independent variables included in the study. A complete overview of the variables is provided in Appendix C, with a description of the Medicaid data files, and the variables included therein, included in Appendix D.

2.4.1 Dependent Variables

2.4.1.1 Medication Compliance

Two components of medication compliance were assessed in this study: adherence and persistence. In measuring compliance, prescriptions for different dosage strengths of a drug filled on the same day were considered to be part of the same prescription. The follow-up period varied by patient and consisted of the time from the index prescription to either the development of diabetes, discontinuation of therapy, switching of therapy to another antipsychotic, addition of another antipsychotic, or end of follow-up data. The two aspects of medication compliance, adherence and persistence, were used as covariates in the logistic regression analysis examining the relationship between antipsychotic use and development of diabetes.

2.4.1.1.1 Adherence to Antipsychotic Therapy

Adherence was assessed using a method called medication possession ratio (MPR). This technique uses prescription redemption records to reflect the number of days that the patient was in possession of their medication and was first described in 1991.³⁷¹ There are a number of assumptions inherent in this technique, the most important of which is that the patient is assumed to have consumed all the medication in their possession prior to obtaining their next refill. MPR was calculated using the following formula:

Figure 2.2: Medication Possession Ratio Calculation³⁷¹

$$\text{MPR} = \frac{\sum \text{Number of days of medication supplied}}{(\text{Date of last refill} + \text{number of days supplied in last prescription}) - \text{Date of first prescription fill}}$$

In order to obtain stable estimates, MPRs were only calculated for patients who obtained at least one prescription refill. In addition to examining mean MPR rates, patients were categorized according to their level of adherence using the following designations: MPR = 0.00 to <0.50, non-adherent; MPR = 0.50 to <0.80, partially adherent; MPR = 0.80 to <1.10, adherent; and MPR > 1.10, excess medication filler.^{341;344;345} As a form of sensitivity analysis, adherence was also calculated using an intent-to-treat approach, whereby it was measured over a 365-day period for all patients filling more than one antipsychotic prescription. That is:

Figure 2.3: Modified Medication Possession Ratio Calculation

$$\text{MPR}_{365 \text{ days}} = \frac{\sum \text{Number of days of medication supplied}}{365}$$

2.4.1.1.2 Persistence with Antipsychotic Therapy

Persistence with therapy was defined as the number of days of continuous therapy during the follow-up period. In calculating persistence, a 50 percent grace-period between prescriptions was allowed.³⁷² For example, patients receiving a 30-day supply were considered to have persisted with therapy if they refilled their prescription within a 45-day (30 x 1.5) window from that date. Patients receiving a 90-day prescription were considered persistent with therapy if they refilled their prescription within a 135-day window. Overall persistence was then calculated using the following formula:

Figure 2.4: Calculation of Persistence³⁷³

$$\text{Persistence} = \Sigma \text{Number of persistent days}$$

As a form of sensitivity analysis, persistence was also calculated using a 100 percent grace-period between prescriptions. That is, a patient was considered persistent if they refilled a 30-day prescription within a 60-day window, or a 90-day prescription within a 180-day window, from the first dispensing date.

2.4.1.2 Prevalence of diabetes

In phase II of the study, the primary dependent variable was the prevalence of diabetes. This was defined as the detection of a medical claim with an ICD-9 code for diabetes (ICD-9 code: 250.0-250.99); or a pharmacy claim for insulin, an insulin sensitizing or glucose lowering agent (sulfonylurea, biguanide, thiazolidinedione, meglitinide or α -glucosidase inhibitor) at the time of study enrollment or in the preceding 180 days.

2.4.1.3 Time to Occurrence of Diabetes

This was defined as the duration of time, in days, from the index prescription date to the date of a new diagnosis of diabetes as defined by this study.

2.4.1.4 Incidence of diabetes

In phase III, the primary dependent variable was the incidence of diabetes. This was defined as a new medical claim with an ICD-9 code for diabetes (ICD-9 code: 250.0-250.99); or a new pharmacy claim or a pharmacy claim for insulin, an insulin sensitizing or glucose lowering agent (sulfonylurea, biguanide, thiazolidinedione, meglitinide or α -glucosidase inhibitor). The date of first recording of one of these events served as the date of diagnosis of new-onset diabetes, and was used to estimate the duration of time to the development of

diabetes. To ensure that only incident cases were included, the event was required to occur at least seven days subsequent to the index antipsychotic prescription. In addition, all patients were prescreened to ensure the absence of diabetes as defined in this study, during the 180 days preceding the index prescription. Finally, to reduce the risk of missing new-onset cases that may have been attributable to antipsychotic therapy, new cases of diabetes detected in the first 30 days after discontinuation of an antipsychotic agent were attributed to that agent. As noted, patients were followed for a maximum of 365 days from the index date.

2.4.2 Independent Variables

In an attempt to control for factors that may confound the relationship between exposure to antipsychotic therapy and the development of diabetes, known and possible risk factors for diabetes were included as independent variables. These variables were categorized as demographic, clinical, or medication variables. The operational definition used for each variable follows.

2.4.2.1 Demographic Variables:

2.4.2.1.1 Age

The reference age used for each study participant was their age in years at the time of first dispensing of an antipsychotic agent. This was included as a continuous variable. Age was also stratified according to the following groupings: 18-34; 35-44; 45-54; 55-64 and age ≥ 65 years.

2.4.2.1.2 Gender

Patient gender was included as a dichotomous variable: ‘male’ or ‘female.’

2.4.2.1.3 Race / Ethnicity

Patients were categorized according to the following racial/ethnic groups: Asian-American; Black; Hispanic-American; Native-American; Pacific Islander; White; and ‘Others.’

2.4.2.2 Clinical Variables

2.4.2.2.1 Mental Disorder Diagnoses

Mental disorders were identified by the International Classification of Diseases, Ninth Revision diagnostic codes (ICD-9) for mental disorders (ICD-9: 290 – 319).³⁷⁴ Patients were also stratified into one of six mutually exclusive, jointly exhaustive categories. These were: schizophrenia disorders; bipolar disorder; dementias; other psychotic disorders; other non-psychotic mental disorders; and ‘no mental health diagnosis.’ These categories were created in consultation with a clinical expert in the field of psychiatry. A description of the conditions contained within each of these groups, together with their ICD-9 codes, is outlined in Appendix E. Patients with a diagnosis of mental retardation (ICD-9: 317-319) were excluded from further analyses because of the difficulty of making accurate diagnoses of other mental disorders in this cohort.

Patients with more than one mental disorder diagnosis were classified according to the following rules. If a patient had medical claims with ICD-9 codes for both schizophrenia and bipolar disorder, the modal diagnosis was used. If these diagnoses were present in equal numbers, the diagnosis closest in time to the index prescription was used. If the patient had medical claims for schizophrenia or bipolar disorder in addition to diagnoses for other psychotic disorders, dementia, or non-psychotic disorders, the patient was classified in terms of their schizophrenia or bipolar diagnosis. That is, a hierarchical approach was taken to the stratification, with other mental disorders being considered to be co-morbid to the primary mental disorder diagnosis of schizophrenia or bipolar

disorder. For example, a patient with diagnoses of schizophrenia, alcoholic psychosis and anxiety disorder was classified as being schizophrenic. A similar approach was adopted for patients who had diagnoses for both other psychotic disorders and non-psychotic disorders (but not schizophrenia or bipolar disorder). It was assumed that these patients received the antipsychotic because of their psychotic condition, and they were, therefore, stratified into the ‘other psychotic conditions’ group. As an example, a patient with diagnoses for both depressive psychoses and anxiety was classified in the ‘other psychotic disorders’ group. Patients with comorbid dementia and non-psychotic disorders were preferentially categorized in the dementia group. As noted earlier, a breakdown of each of the mental disorders by ICD-9 code included in each of the five diagnostic categories is included in Appendix E.

2.4.2.2.2 Hypertension

This was included as a dichotomous variable: ‘no hypertension’ or ‘hypertension.’ A diagnosis of hypertension was defined as a medical claim with an ICD-9 code of 401.x to 405.x.

2.4.2.2.3 Dyslipidemia

Dyslipidemia was defined as a medical claim with an ICD-9 code for dyslipidemia (ICD-9 code: 272.0 to 272.4), or a pharmacy claim for lipid lowering therapy. A list of these therapies is included in Appendix F. Using these specifications, dyslipidemia was included as a dichotomous variable, that is, ‘no dyslipidemia’ or ‘dyslipidemia.’

2.4.2.3 Medication Variables

Exposure to an antipsychotic was inferred from a pharmacy claim for one of these agents, identified on the basis of their National Drug Code (NDC) medication class code. The first identified antipsychotic claim served as the

index prescription, with the proviso that no other antipsychotic was issued in the preceding 180 days. As noted previously, patients receiving more than one antipsychotic on the index date, regardless of antipsychotic class, were not included in this study. Commencement of a second antipsychotic agent, switching of treatment to another agent or discontinuation of antipsychotic treatment constituted a study endpoint.

2.4.2.3.1 Antipsychotic Class

Antipsychotic agents were classified as first-generation (Table 2.1), or second-generation agents (clozapine, olanzapine, quetiapine, risperidone, ziprasidone).

Table 2.1: FDA Approved First-Generation Antipsychotic Agents

Chlorpromazine	Perphenazine
Fluphenazine	Pimozide
Haloperidol	Thioridazine
Loxapine	Thiothixene
Mesoridazine	Trifluoperazine
Molindone	

2.4.2.3.2 Antipsychotic Agent

Patients receiving treatment with a second-generation agent were further classified according to the specific agent they received, that is, clozapine, olanzapine, quetiapine, risperidone or ziprasidone.

2.4.2.3.3 Dose

The daily dose of antipsychotic for any given prescription dispensed was inferred from the product of the quantity and strength of the drug dispensed divided by the number of days supplied. For example, if a patient received 60, three milligram risperidone tablets and had an entry of ‘30’ in the ‘days supply’ field, it was inferred that their daily dose of risperidone was six milligrams. Mean

and median daily doses were then calculated and examined for appropriateness based on achievable doses given known product preparation availability. For example, it is inconceivable that doses representing less than a half of a tablet could be administered (i.e., a mean daily dose of risperidone less than 0.125mg, given the smallest available tablet size of 0.25mg). Similarly, taking more than ten tablets a day of a given preparation is unlikely. Any inferred doses falling outside these dosage ranges were examined for coding errors. In consultation with a clinical expert in psychiatry, extreme maximum daily doses for each agent were defined based on knowledge of prescribing practices in this field. For the purpose of this study, the accepted mean daily dose for each agent, therefore, ranged from a minimum of half the lowest tablet strength available for that agent, to the maximum defined by the clinical expert (Table 2.2).

Table 2.2: Available Product Strengths and Mean Daily Dose Ranges Considered for the Second-Generation Antipsychotic Agents

Agent	Available Tablet Strengths	Dose Range
Clozapine ³⁶	25mg, 100mg	12.5mg – 1600mg
Olanzapine ³⁷	2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg	1.25mg – 80mg
Quetiapine ³⁸	25mg, 100mg, 200mg, 300mg	12.5mg – 2400mg
Risperidone ³⁹	0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg	0.125mg – 16mg
Ziprasidone ⁴⁰	20mg, 40mg, 60mg, 80mg	20mg* – 260mg

* Minimum strength available is a 20mg capsule.

Calculated mean daily doses for antipsychotics falling outside this range were excluded from analyses to prevent the undue influence of outliers, and to minimize the impact of coding errors. As a form of sensitivity analysis, mean (median) daily doses were also calculated taking into account gaps in patient therapy (which were presumably due to non-adherence). For example, a patient receiving three, thirty-day prescriptions for risperidone three milligrams over a 110-day period (that is, with two 10-day gaps between refill prescriptions) would

have a calculated mean daily dose of 2.45 milligrams (3x30x3/110) compared to a calculated dose of 3 milligrams (3x30x3/90) using the former method of calculating mean daily dose.

To facilitate dose-based comparisons between the second-generation antipsychotic agents, patients were classified as receiving ‘Low,’ ‘Medium,’ or ‘High’ dose antipsychotic therapy based on their derived mean daily dose of antipsychotic. These strata were developed in consultation with a clinical expert in psychiatry and were based on the therapeutic efficacy of the agents (Table 2.3). As discussed in section 1.10.4 (Chapter 1), lower doses of antipsychotics are typically recommended in elderly patients due to differences in the efficacy and tolerability of these agents in this population. A modified dose stratification was, therefore, also used for patients aged 65 years or older (Table 2.3).

Table 2.3: Classification of Mean Daily Dose (Milligrams) of Olanzapine, Quetiapine and Risperidone as ‘Low,’ ‘Medium,’ or ‘High’ Dose Therapy and Modified Classification for Patients Aged 65 Years or Older

Agent	Olanzapine	Quetiapine	Risperidone
All Patients			
Low Dose	≤ 10	≤ 300	≤ 2
Medium Dose	>10 - 15	>300 – 600	>2 – 6
High Dose	> 15	> 600	> 6
≥ 65 Years			
Low Dose	≤ 5	≤ 100	≤ 0.5
Medium Dose	5 - 10	>100 – 300	>0.5 – 1.5
High Dose	> 10	> 300	> 1.5

2.4.2.3.4 Duration of Antipsychotic Treatment

The duration of treatment of the antipsychotic was inferred from the sum of the number of days supplied. A patient was considered to have discontinued

treatment if a refill for the prescription did not occur within a specified timeframe (i.e., refill of the prescription during the time covered by the existing prescription plus a 50% grace-period). For example, if a prescription was for a 30-day supply, it was assumed that the treatment was discontinued if no refill occurred within 45 days (30×1.5) of dispensing. As an additional sensitivity analysis, the duration of therapy was also calculated allowing for a 100 percent grace-period between prescriptions (e.g., a patient with a 30-day prescription was considered to have discontinued therapy if they did not refill the prescription within 60 days of this being dispensed). Duration of therapy and persistence with therapy were synonymous terms, with the exception that persistence was only calculated for patients filling more than one antipsychotic prescription.

2.4.2.3.5 Concomitant Diabetogenic Medications

Certain agents are known to increase the risk of diabetes and had the potential to confound the study. These included: β -adrenergic blockers; glucocorticoids; oral contraceptive pills containing norgesterol; phenytoin; thiazide diuretics and valproic acid.²⁰⁴ Consideration was given only to concurrent prescriptions for any of these agents. Data were dichotomized on the basis of presence (1) or absence (0) of any one of the drug classes here listed.

2.4.2.4 Unavailable Variables

Several variables known to increase the risk of diabetes were not included in this study as this information was not available in the Medicaid database. These included a family history of diabetes, measures of weight, body mass index, central adiposity, and lifestyle issues such as a sedentary lifestyle or consumption of a high caloric diet. The absence of this information represents a limitation of this study.

2.5 Sample Size Calculations

To determine the minimum sample size required in a cohort study, four pieces of information are required: 1) the desired type I error rate, α , including details of its use for one-tailed or two-tailed statistical analyses; 2) the desired type II error rate; 3) the incidence of disease in the unexposed population; and 4) the relative risk of disease in the exposed population that it is important to detect. In this study, the type I error rate (α -level) was set at 0.05 for all statistical analyses. Although larger or smaller values can be used, 0.05 is conventionally used in cohort studies. Likewise, the maximal type II error rate (β -level) viewed to be acceptable was 0.2, giving a minimum accepted power level of 0.8 (i.e., $1-\beta$). Again, by convention, a type II error rate of 0.2 is commonly used in cohort studies. The incidence of diagnosed diabetes among adults aged 18 to 79 years was estimated to be 7.0 per 1,000 population in the U.S. in 2000.³⁷⁵ Of note, this incidence is dependent on age, gender and race/ethnicity with a higher incidence noted in older adults, males and among Blacks and Hispanics.³⁷⁵ The highest incidence of diagnosed diabetes in 2002 was among men aged 45 to 64 years with 13.5 new cases per 1,000 population noted (compared to 12.0 new cases per 1,000 population for women of a similar age).³⁷⁵ As the majority of patients within the dataset were older adults; an incidence of 12.5 per 1,000 population was arbitrarily selected, as opposed to the national average, to reflect the study population. Based on the available literature, the relative risk of developing diabetes ranged from 1.05–4.97* in patients treated with first-generation antipsychotics and from 0.9–4.7* for those treated with second-generation antipsychotics compared to those not treated with antipsychotics.^{3;4;9;10;232;236-238} Similarly, when compared to patients treated with first-generation antipsychotics, the relative risk of developing diabetes ranged from 1.0–2.6* for those treated with a second-generation agent.^{4;241;243;246;250} To be conservative,

and taking into consideration the minimum accepted relative risk to determine clinical significance, a relative risk of 2.0 was selected.³⁷⁵ This ratio of exposed to unexposed study subjects impacts the statistical power of the study, with an equal number of exposed to unexposed subjects required to obtain an 80 percent power of detecting an effect.³⁷⁵ Further increases in the size of the unexposed group compared to the exposed group, for example from 1:1 to 2:1 to 3:1, provides progressively smaller gains in statistical power while greatly increasing the sample size required.³⁷⁵ In this study, the ratio of exposed to unexposed study subjects was set at 1:1.

A number of different formulae have been used to estimate sample size based on the parameters specified above. One commonly used formula in cohort studies is:

Figure 2.5: Sample Size Calculation³⁷⁵

$$N = \frac{1}{p[p(1-R)]^2} \left[Z_{1-\alpha/2} \sqrt{\left(1 + \frac{1}{K}\right)U(1-U)} + Z_{1-\beta} \sqrt{pR \left(1 - Rp\right) + \frac{p(1-p)}{K}} \right]^2$$

where p is the incidence of the disease in the unexposed population, R is the minimum relative risk, α is the type I error rate, β is the type II error rate, $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are the unit normal deviates corresponding to α (two-tailed testing) and β , and K is the ratio of control subjects to the number of exposed subjects.³⁷⁵

Finally U is defined as:

Figure 2.6: Definition of U in Sample Size Calculation³⁷⁵

$$U = \frac{Kp + pR}{K + 1}.$$

Using these defined parameters, the number of subjects required in each comparison group was 1,927 in two-tailed analyses.

2.6 Data Collection

As noted, this was a retrospective database analysis using electronic medical and prescription records of Texas Medicaid enrollees aged 18 years or older, who received antipsychotic medications. Medicaid enrollee and clinical data were collected with the assistance of the Research and Forecasting Department of the Texas Health and Human Services Commission (THHSC). Data included age, gender, race/ethnicity and information on mental disorder, hypertension and diabetes-related medical claims as identified by ICD-9 codes. Medicaid pharmacy data were collected, with the permission of the THHSC, from The University of Texas at Austin, which is licensed to use these data. Pertinent data from the pharmacy databases included age, gender, date of service and information on the medications dispensed. Unique identifiers assigned to the patient-level data were used to merge the various data files. Appendix D includes a description of the Medicaid data files and the variables included therein.

2.7 Data Analyses

All data manipulation, descriptive and inferential statistical analyses were performed using SPSS software (version 13.0 for Windows, Chicago, 2004) and Visual FoxPro software. A preliminary examination of the data was conducted using frequencies for each variable to check for data abnormalities. Statistical analyses appropriate for testing the stated hypotheses were used. All statistical analyses were two-tailed, with statistical significance set *a priori* at 0.05. Differences in demographic and clinical variables were analyzed as follows. Categorical variables, such as gender, were examined using chi-square tests. Continuous variables such as age and duration of follow-up were examined for normality and analyzed using Student's t-tests or analysis of variance (ANOVA) or, if violating the assumption of normality, with the Mann-Whitney or Kruskal-Wallis tests, respectively. Post-hoc analyses to investigate significant differences

in ANOVA tests were conducted as appropriate. The Scheffé test was used where sample sizes differed, but group variances were equal. The Games-Howell test was used in instances where both sample size and group variances were unequal.

2.7.1 Medication Compliance

As noted previously, two components of medication compliance were assessed in this study: adherence and persistence, with adherence being assessed using the medication possession ratio (MPR) method. Bivariate analyses were conducted comparing mean (median) MPR rates according to demographic variables (age, gender, ethnicity), by class of antipsychotic (first-generation vs. second-generation), by the specific second-generation antipsychotic (clozapine, olanzapine, quetiapine, risperidone and ziprasidone) and by primary mental disorder diagnosis (schizophrenia, bipolar disorders, other psychotic disorders, dementias, other non-psychotic mental disorder diagnoses, and no mental health diagnosis). In addition, patients were categorized and compared according to their level of adherence using the following designations: MPR = 0 to < 0.5, non-adherent; MPR = 0.50 to <0.8, partially adherent; MPR = 0.80-1.10, adherent; and MPR > 1.10, excess medication filler. Mean MPR rates were compared using the Student's t test or ANOVA (or if violating the assumption of normality, with the Mann-Whitney test) as appropriate. Post-hoc analyses to investigate significant differences in ANOVA tests were conducted where necessary.

As with adherence, bivariate analyses were conducted examining differences in mean persistence rates according to patient demographic variables, by class of antipsychotic (first-generation vs. second-generation), by specific second-generation antipsychotic (clozapine, olanzapine, quetiapine, risperidone and ziprasidone) and by primary mental disorder diagnosis (schizophrenia, bipolar disorders, other psychotic disorders, dementias, other non-psychotic mental disorder diagnoses, and no mental health diagnosis). The statistical

techniques used to make these comparisons were as for those used to compare adherence rates.

Adherence and persistence with antipsychotic therapy were used as covariates in the logistic regression analysis examining the relationship between antipsychotic use and development of diabetes.

2.7.2 Prevalence of Diabetes

The prevalence of diabetes was defined as the number of cases of prevalent diabetes as a percentage of eligible patients. This definition applied regardless of the stratification used: age; gender; race/ethnicity or primary mental disorder diagnosis. Despite the fact that patients may have had multiple mental disorder diagnoses during the study period, all patients were classified according to their primary mental disorder diagnosis, as defined for the purpose of this study. Additional or secondary mental disorder diagnoses were not considered when prevalence rates were examined. Patients could, therefore, only contribute as a single case to the denominator for each of the strata examined: age; gender; race/ethnicity or primary mental disorder diagnosis. Comparison of prevalence rates between strata were examined using the Pearson chi-square test. In addition, patients were dichotomized into two groups: those with a diagnosis of diabetes during the study period; and those without, and logistic regression analyses were used to assess the prevalence of diabetes after controlling for demographic (i.e., age, gender, race/ethnicity), and clinical (i.e., primary mental disorder diagnosis, hypertension, dyslipidemia) risk factors for diabetes. This is the preferred method of biostatistical analysis because of its robustness against violations of multivariate normality.³⁷⁶ This method of analysis allows multiple comparisons to be made without inflation of the type I error rate of the study.³⁷⁶ Variables with high correlations were assessed to avoid multicollinearity. The following model was used:

Figure 2.7: Regression Model³⁷⁶

$$\hat{Y}_i = \frac{e^u}{1 + e^u}$$

Where \hat{Y}_i was the estimated probability of individual i developing diabetes and u was the linear combination

Figure 2.8: Definition of U for the Regression Model³⁷⁶

$$u = B_0 + B_1X_1 + B_2X_2 +B_kX_k$$

with constant B_0 , coefficients B_j and predictors X_j for k predictors ($j = 1, 2, \dots, k$). Taking the natural logarithm of both sides, the model was rewritten as:

Figure 2.9: Logistic Regression Model³⁷⁶

$$\ln\left(\frac{\hat{y}}{1 - \hat{y}}\right) = B_0 + \sum B_j X_{ij}$$

Where the odds of developing diabetes for an individual i , depended on the value of the constant B_0 , as well as the contribution of the variables used in the model. The variables included in the study model are outlined in Appendix G. Using this model, one hypothesis was tested: that the prevalence of diabetes did not differ based on primary mental health diagnosis, after controlling for all other variables.

2.7.3 Time to Occurrence of Diabetes

The time to occurrence of diabetes was compared between the first- and second-generation antipsychotics (as groups), and among the individual second-generation antipsychotics. The Cox proportional hazards regression model was used in these analyses to estimate survival. This method describes the time-to-event for all observations, predicts the association between a set of independent variables (continuous or categorical) and a dependent variable, and has the

advantage of allowing the use of censored data.³⁷⁷ The data in this study were right-censored, in that the outcome of interest (i.e., development of diabetes) may not have occurred during the study follow-up period. That is, data were considered censored for any patient who did not develop diabetes and for whom the study endpoint was the discontinuation or switching of antipsychotic therapy, or who had not developed diabetes by the end of the study follow-up period. This method examines the cumulative probability of surviving (i.e., remaining diabetes-free) over time, and provides an unbiased estimate of this survival time when censored data are being used.³⁷⁷

2.7.4 Incidence of diabetes

Phase III of the study related to the incidence of diabetes and was defined as the number of new-onset cases of diabetes as a percentage of the number of eligible patients. As outlined in the inclusion criteria, to be eligible for this phase of the study, patients were required to meet an additional criterion, that is, no history of diabetes in the 180 days prior to study enrollment. This applied regardless of the stratification used: age; gender; race/ethnicity; primary mental health diagnosis; class of antipsychotic or specific type of second-generation antipsychotic used. Comparisons of incidence rates between strata were examined using the Pearson chi-square test. Logistic regression analysis was used to determine the relative odds of diabetes according to the specific second-generation antipsychotic agent after adjusting for demographic, clinical and medication variables. Patients were again dichotomized into two groups: those developing diabetes during the study period; and those who did not. Three study models were developed. Model 1 tested the hypothesis that the incidence of diabetes did not differ based on class of antipsychotic agent, while controlling for all other variables. Model 2 tested the hypothesis that the incidence of diabetes did not differ according to the specific type of second-generation antipsychotic

used (olanzapine, quetiapine or risperidone), while controlling for all other variables. Model 3 tested six hypotheses, that is, that the incidence of diabetes did not differ according to the dose of antipsychotic used, for each of the three different second-generation antipsychotic agents (olanzapine, quetiapine, risperidone) and that the incidence of diabetes did not differ according to the primary mental diagnosis for each of the three different second-generation antipsychotic agents, while controlling for other variables. The variables included in each of these study models are outlined in Appendix H. No patient received ziprasidone as their index antipsychotic agent, and the use of clozapine was limited; therefore, regression analysis was not performed for these agents.

2.7.5 Hypothesis Testing and Associated Statistical Methods

Table 2.4 contains a summary of the hypotheses that were tested in this study, the study measures used for each hypothesis and the statistical techniques used to test the hypotheses.

Table 2.4: Hypotheses Tested, Study Measure(s) and Statistical Techniques

Hypothesis	Study Measure	Statistical Technique
<i>Phase 1: Epidemiology and Antipsychotic Utilization Patterns (Objective 1)</i>		
H _{0(1a)} : The percentage of patients receiving treatment with the different antipsychotic agents will not differ significantly when stratified according to patient age.	Agent (class) specific prevalence of antipsychotic use	Pearson Chi-square (χ^2)
H _{0(1b)} : The percentage of patients receiving treatment with the different antipsychotic agents will not differ significantly when stratified according to patient gender.	Agent (class) specific prevalence of antipsychotic use	Pearson Chi-square (χ^2)
H _{0(1c)} : The percentage of patients receiving treatment with the different antipsychotic agents will not differ significantly when stratified according to patient race/ethnicity.	Agent (class) specific prevalence of antipsychotic use	Pearson Chi-square (χ^2)
H _{0(1d)} : The percentage of patients receiving treatment with the different antipsychotic agents will not differ significantly when stratified according to patient primary mental health diagnosis.	Agent (class) specific prevalence of antipsychotic use	Pearson Chi-square (χ^2)
<i>Phase 1: Epidemiology and Antipsychotic Utilization Patterns (Objective 2)</i>		
H _{0(2a)} : The classification of mean daily antipsychotic dose as ‘Low,’ ‘Medium,’ or ‘High’ will not differ significantly when stratified according to the second-generation antipsychotic (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) used.	Categorized mean daily dose of the specific second-generation antipsychotics	Pearson Chi-square (χ^2)
H _{0(2b-f)} : The mean daily dose for the second-generation antipsychotics (clozapine (2b) olanzapine (2c), quetiapine (2d), risperidone (2e), and ziprasidone (2f)) will not differ significantly when stratified according to patient age.	Mean daily dose of the specific second-generation antipsychotics stratified by age	ANOVA
H _{0(2g-k)} : The mean daily dose for the second-generation antipsychotics (clozapine (2g), olanzapine (2h), quetiapine (2i), risperidone (2j), ziprasidone (2k)) will not differ significantly when stratified according to the primary mental health diagnosis.	Mean daily dose of the specific second-generation antipsychotics stratified by diagnosis	ANOVA

Table 2.4: Hypotheses Tested, Study Measure(s) and Statistical Techniques (continued)

Hypothesis	Study Measure	Statistical Technique
<i>Phase 1: Epidemiology and Antipsychotic Utilization Patterns (Objective 2 continued)</i>		
H _{0(3a)} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient age.	Age-specific adherence with antipsychotic therapy	ANOVA
H _{0(3b)} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient age.	Age-specific persistence with antipsychotic therapy	ANOVA
H _{0(3c)} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient gender.	Gender-specific adherence with antipsychotic therapy	ANOVA
H _{0(3d)} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient gender.	Gender-specific persistence with antipsychotic therapy	ANOVA
H _{0(3e)} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient race/ethnicity.	Race/ethnicity-specific adherence with antipsychotic therapy	ANOVA
H _{0(3f)} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient race/ethnicity.	Race/ethnicity-specific persistence with antipsychotic therapy	ANOVA
H _{0(3g)} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient primary mental health diagnosis.	Diagnosis-specific adherence with antipsychotic therapy	ANOVA
H _{0(3h)} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient primary mental health diagnosis.	Diagnosis-specific persistence with antipsychotic therapy	ANOVA
H _{0(3i)} : Adherence with antipsychotic therapy will not differ significantly when stratified according to the antipsychotic agent prescribed.	Agent-specific adherence with antipsychotic therapy	ANOVA
H _{0(3j)} : Persistence with antipsychotic therapy will not differ significantly when stratified according to the antipsychotic agent prescribed.	Agent-specific persistence with antipsychotic therapy	ANOVA

Table 2.4: Hypotheses Tested, Study Measure(s) and Statistical Techniques (continued)

Hypothesis	Study Measure	Statistical Technique
Phase II: Prevalence of Diabetes (Objective 3)		
H _{0(4a)} : The prevalence of diabetes will not differ significantly according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Diagnosis-specific prevalence of diabetes	Pearson Chi-square (χ^2)* Logistic regression
Phase III: Incidence of Diabetes (Objective 4)		
H _{0(5a)} : The time to occurrence of diabetes will not differ significantly according to the class of antipsychotic agent (first or second-generation) used, after controlling for demographic, clinical and medication risk factors for diabetes.	Class-specific time to occurrence of diabetes	Student T-Test* Cox Proportional Hazards Regression Analysis
H _{0(5b)} : The time to occurrence of diabetes will not differ significantly according to the specific second-generation antipsychotic used, after controlling for demographic, clinical and medication risk factors for diabetes.	Agent-specific time to occurrence of diabetes	ANOVA* Cox Proportional Hazards Regression Analysis
H _{0(6a)} : The incidence of diabetes will not differ significantly according to the class of antipsychotic agent used (first or second-generation) after controlling for demographic, clinical and medication risk factors for diabetes.	Class-specific incidence of diabetes	Pearson Chi-square (χ^2)* Logistic regression
H _{0(6b)} : The incidence of diabetes will not differ significantly according to the specific second-generation antipsychotic agent used after controlling for demographic, clinical and medication risk factors for diabetes.	Agent-specific incidence of diabetes	Pearson Chi-square (χ^2)* Logistic regression
H _{0(7a-e)} : The incidence of diabetes will not differ significantly according to the dose used for the second-generation antipsychotic agents (clozapine (7a), olanzapine (7b), quetiapine (7c), risperidone (7d), ziprasidone (7e)) after controlling for demographic, clinical and medication risk factors for diabetes.	Dose-specific incidence of diabetes	Pearson Chi-square (χ^2)* Logistic regression
H _{0(8a-e)} : The incidence of diabetes will not differ significantly according to the primary mental disorder diagnosis for the second-generation antipsychotic agents (clozapine (8a), olanzapine (8b), quetiapine (8c), risperidone (8d), ziprasidone (8e)) after controlling for demographic, clinical and medication risk factors for diabetes.	Indication-specific incidence of diabetes	Pearson Chi-square (χ^2)* Logistic regression

* Refers to bivariate analysis

Chapter 3: Results

This chapter details the results of the study, and includes a description of the study population and analysis of each of the study objectives. Patients who filled at least one prescription for an antipsychotic agent were identified using electronic medical records over a five-year period from January 1, 1997 to December 31, 2001, as depicted in Figure 2.1, Chapter 2. The date of the first antipsychotic prescription was selected as the index date. These patients were followed for a maximum of 12 months from the index date until a study endpoint occurred, with each patient eligible for enrollment in the study on one occasion only. The study sample consisted of 19,430 Texas Medicaid enrollees. The study was divided into three phases: phase I described demographic and antipsychotic utilization patterns; phase II described the prevalence of diabetes; and phase III described the incidence of diabetes in the study population. Eligibility criteria for the study were: 1) age 18 years or older; 2) receipt of a first- or second-generation antipsychotic agent, but having a six-month (180-day) antipsychotic-free window prior to the identification of the index prescription; 3) continuous enrollment for six months prior to, and 12 months subsequent to the index date; with 4) evidence of at least one medical claim in this time. The study was limited to patients receiving antipsychotic monotherapy, with an additional restriction for phase III of the study that the patients not have a history of diabetes at the time of study enrollment, or in the preceding six months. Table 3.1 outlines the study's exclusion criteria with the corresponding sample size remaining after the implementation of each criterion.

Table 3.1: Study Exclusion Criteria and Sample Size

Exclusion Criteria	Excluded	Sample Size
Patients receiving an antipsychotic prescription		129,860
Age < 18 years	9,090	120,770
No antipsychotic-free window ¹	78,796	41,974
Not continuously enrolled ²	18,261	23,713
Absence of a medical claim ³	4,046	19,667
Combination antipsychotic therapy ⁴	237	19,430
Phases I & II		
Study sample size		19,430
Preexisting diabetes ⁵	3,293	16,137
Phase III		
Study sample size		16,137

¹. No antipsychotic dispensed in six-months prior to index prescription date.

² For six-months prior to, and 12-months post the index prescription date.

³ Minimum one medical claim in the six-months prior to, or 12-months post the index prescription date.

⁴ Receiving more than one antipsychotic agent on the index date.

⁵ History of diabetes in the six months prior to, or six days post the index date.

The results of the study are presented in order of the study objectives and in accordance with the relevant study phase, i.e.:

- Phase I: Epidemiology and Antipsychotic Utilization Patterns (Objectives 1-2);
- Phase II: Prevalence of Diabetes (Objective 3);
- Phase III: Incidence of Diabetes (Objective 4).

Within each section, the hypotheses and associated statistical analyses are presented.

3.1 Phase I: Epidemiology and Antipsychotic Utilization Patterns

Three categories of independent study variables were examined: demographic, clinical and medication-related variables. The demographic variables examined were the age, gender and race/ethnicity of the study participants. The clinical variables comprised: primary mental health diagnosis, and diagnosis of hypertension or dyslipidemia. Medication variables included: class of antipsychotic; specific second-generation antipsychotic used; mean daily antipsychotic dose; compliance with antipsychotic therapy; duration of antipsychotic therapy and use of concomitant diabetogenic medications.

3.1.1 Demographic Variables

Demographic characteristics available from patient medical records were age, gender and race/ethnicity. The statistics to describe these variables are discussed below, with the data shown in Tables 3.2 to 3.5.

3.1.1.1 Age and Gender (Objective 1)

The average patient age was 60.3 years (SD: 21.9). As specified in the inclusion criteria, patients were required to be 18 years or older at the index date. In accordance with HIPAA regulations, age data for patients aged greater than 89 years were collapsed to a maximum value of 89 years. When stratified according to the age groupings: 18-34; 35-44; 45-54; 55-64; and ≥ 65 , the majority of patients (47.6%) were 65 years or older (Table 3.2). Patients were approximately equally distributed between the first three strata, with these strata accounting for 44.3 percent of the overall cohort. As illustrated in Table 3.3, approximately two-thirds of the population was female.

Table 3.2: Age Distribution in the Texas Medicaid Study Population

Age Group (Years)	N	Percent (%)
18-34	2,835	14.6
35-44	3,063	15.8
45-54	2,700	13.9
55-64	1,581	8.1
≥ 65	9,251	47.6
Total	19,430	100.0

Table 3.3: Gender Distribution in the Texas Medicaid Study Population

Gender	N	Percent (%)
Male	6,659	34.3
Female	12,771	65.7
Total	19,430	100.0

A bivariate analysis of age and gender revealed that patient age differed significantly by gender. Male enrollees were significantly younger ($t=-37.469$, $df=19,428$, $p<0.001$) than their female counterparts, with a mean age of 52.4 years (SD: 21.5) for men compared to 64.4 years (SD: 21.0) for women.

3.1.1.2 Race/Ethnicity (Objective 1)

Table 3.4 outlines the racial/ethnic distributions of the study population. The majority of enrollees were White (55.1%), with Blacks the next largest racial/ethnic group (21.4%), followed by Hispanics (16.4%).

Table 3.4: Race/Ethnicity Distribution in the Texas Medicaid Study Population

Race/Ethnicity	N	Percent (%) ¹
White	10,712	55.1
Black	4,148	21.4
Hispanic	3,190	16.4
Native American	55	0.3
Asian	127	0.7
Other	1,198	6.2
Total	19,430	100.1

¹. Percentage does not add to 100.0, due to rounding.

In a bivariate analysis of race and age, the mean age of enrollees differed significantly ($F=361.953$, $df=3$, $p<0.001$) according to race/ethnicity with White enrollees being the oldest (Table 3.5). Post-hoc analyses revealed significant differences ($p<0.001$) between all possible contrasts.

Table 3.5: Distribution of Race/Ethnicity by Age in the Texas Medicaid Study Population

Race/Ethnicity	Mean Age (Years) ¹	SD ²
White	64.3	21.9
Black	53.8	20.3
Hispanic	59.7	21.1
Native American/Asian/Other	49.9	20.2
All	60.3	21.9

¹. $p<0.001$ for both ANOVA and Kruskal-Wallis tests.

². Abbreviations: SD – Standard Deviation.

The race/ethnicity of the study population also differed significantly by gender ($\chi^2=94.225$, $df=3$, $p<0.001$). For example, women accounted for only 60.1 percent of Hispanic enrollees compared to 68.1 percent of White enrollees.

3.1.2 Clinical Variables

Clinical factors with the potential to confound the relationship between exposure to an antipsychotic and development of diabetes were examined in the study. Descriptive statistics for each of the variables are outlined below, with summary data outlined in Tables 3.6 to 3.8.

3.1.2.1 Primary Mental Health Diagnosis (Objective 1)

Mental health diagnoses were identified using ICD-9 diagnostic codes, a breakdown of which is included in Appendix E. Patients were stratified into one of five mutually exclusive, jointly exhaustive categories in accordance with the criteria outlined in section 2.4.2.2.1 (Chapter 2). Patients with a diagnosis of mental retardation were excluded from further analyses because of the difficulty in making accurate diagnoses of other mental disorders in this cohort. Two thousand, two hundred patients (11.3%) had a diagnosis of mental retardation. Thirty-one percent of the remaining 17,230 of enrollees had no mental health diagnosis. Whereas antipsychotics are only approved for use in schizophrenia and bipolar disorder, only 16.5 percent of enrollees were classified as having schizophrenia with a further 15.5 percent classified as having bipolar disorder (Table 3.6).

Approximately one-third of the enrollees (32.1%) had more than one type of mental health diagnosis. For example, among patients classified as having schizophrenia, 52.8 percent had at least one other type of mental health diagnosis, with 37.4 percent having two other types of mental health diagnoses. Common comorbid mental health conditions are outlined in Table 3.7.

Table 3.6: Frequency Distribution of Primary Mental Health Diagnoses in the Texas Medicaid Study Population

Diagnostic Category	N	Percent (%) ²
Schizophrenia	2,836	16.5
Bipolar Disorder	2,678	15.5
Dementia	2,465	14.3
Psychotic Disorder	1,402	8.1
Non-Psychotic Disorder	2,503	14.5
No Mental Health Diagnosis	5,346	31.0
Total	17,230¹	99.9

^{1.} N=2,200 Medicaid enrollees (11.3%) with diagnosis of mental retardation excluded.

^{2.} Percentage does not add to 100.0, due to rounding.

Table 3.7: Frequency of Comorbid Mental Health Conditions for Texas Medicaid Enrollees Stratified according to Primary Mental Health Category

Categorized As ¹ :	Comorbid Condition(s) (%)				
	Schizophrenia	Bipolar	Dementia	Psychotic Disorder	Non-Psychotic Disorder
Schizophrenia	100.0	13.1 ²	3.1	11.4	45.8
Bipolar Disorder	11.6 ²	100.0	9.6	14.1	66.6
Dementia	N/A	N/A	100.0	32.3	43.1
Psychotic Disorder	N/A	N/A	N/A	100.0	43.6
Non-Psychotic Disorder	N/A	N/A	N/A	N/A	100.0

^{1.} All patients categorized according to hierarchical process.

^{2.} As Schizophrenia and Bipolar Disorder are not comorbid conditions, status reflects probable diagnostic uncertainty.

3.1.2.2 Hypertension (Objective 1)

Hypertension was included as a dichotomous variable: ‘no hypertension,’ or ‘hypertension,’ and was defined as a medical claim with an ICD-9 code for hypertension. Overall, 24.9 percent of the population was defined as being hypertensive.

3.1.2.3 Dyslipidemia (Objective 1)

Dyslipidemia was defined as a medical claim with an ICD-9 for dyslipidemia, or a pharmacy claim for lipid lowering therapy. Using these specifications, it was included as a dichotomous variable: ‘no dyslipidemia,’ or ‘dyslipidemia,’ and accordingly 9.2 percent of the population was defined as having dyslipidemia (Table 3.8).

Table 3.8: Diagnosis of Dyslipidemia in the Texas Medicaid Study Population

Diagnosis	N	Percent (%)
Dyslipidemia	1,790	9.2
Identified by:		
ICD-9 code only ¹	731	3.8
Rx only ¹	741	3.8
ICD-9 code and Rx ¹	318	1.6
No Dyslipidemia	17,640	90.8
Total	19,430	100.0

¹. Abbreviations: ICD-9 - International Classification of Diseases, Ninth revision; Rx - Prescription for lipid lowering medication.

3.1.3 Medication Variables

3.1.3.1 Concomitant Diabetogenic Medications (Objective 1)

Several classes of medications are known to increase the risk of diabetes and had the potential to confound this study. Overall, 26.2 percent of the population received a concomitant diabetogenic medication during the interval between their index antipsychotic prescription and their study endpoint. The frequency distribution of patients who received concomitant diabetogenic medications is illustrated in Table 3.9.

Table 3.9: Percentage of Texas Medicaid Study Population Treated with Concomitant Diabetogenic Medications

Concomitant Diabetogenic Medications	N	%
Beta-adrenergic-blocker	1,228	6.3
Glucocorticoid	646	3.3
Oral contraceptive agent containing norgesterol	176	0.9
Phenytoin	988	5.1
Thiazide diuretic	1,103	5.7
Valproic acid	1,821	9.4
Total¹	5,099	26.2

¹. Categories were not mutually exclusive; therefore, the total represents the percentage of the population that received one or more classes of a concomitant diabetogenic medication.

3.1.3.2 Antipsychotic Medication Class and Specific Type (Objective 2)

This study examined the use of antipsychotic monotherapy, whereby exposure was inferred from a pharmacy claim for one of these agents. The first identified antipsychotic agent was considered to be the index agent with the proviso that no other antipsychotic was dispensed in the preceding 180 days. A first-generation antipsychotic was prescribed as index therapy to 29.3 percent of the population, with haloperidol the most commonly used (52.3%) of these agents (Table 3.10). Risperidone was the most commonly used second-generation agent, accounting for 42.2 percent of all antipsychotic therapy and approximately 60 percent of all second-generation antipsychotic therapy (Table 3.10). Clozapine was infrequently used, and no patient received ziprasidone as their index agent.

Table 3.10: Frequency Distribution of Index Antipsychotic Therapy for the Texas Medicaid Study Population

Antipsychotic Class (Agent)	N	Percent (%)
First-Generation Agent ¹	5,699	29.3
Second-Generation Agent	13,731	70.7
Clozapine	93	0.5
Olanzapine	4,199	21.6
Quetiapine	1,231	6.3
Risperidone	8,208	42.2
Total	19,430	100.0

¹. First-generation agents included: Chlorpromazine; Fluphenazine; Haloperidol; Loxapine; Mesoridazine; Molindone; Perphenazine; Pimozide; Thioridazine; Thiothixene and Trifluoperazine.

3.1.3.2.1 Use of Specific Antipsychotic Agents According to Age

H_{1a}: The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient age.

A significant difference was noted in a Chi-square analysis testing the relationship between choice of index antipsychotic agent and patient age ($\chi^2 = 416.748$, $df=16$, $p<0.001$). While quetiapine use did not vary by age strata (range 6.2% to 6.6%), use of other agents varied considerably (Table 3.11). In particular, the percentage of patients treated with risperidone varied from 34.6 percent for those aged between 35 and 44 years, to 48.3 percent of those aged 65 years or older. Compared to their younger counterparts, patients age 65 years or older were less likely to receive clozapine, olanzapine or a first-generation antipsychotic, but more likely to receive risperidone (Table 3.11).

H_{1a}: Rejected.

3.1.3.2.2 Use of Specific Antipsychotic Agents According to Gender

H_{1b}: The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient gender.

As seen in Table 3.11, Chi-square analysis showed a significant relationship between choice of index antipsychotic agent and patient gender ($\chi^2 = 76.901$, $df=4$, $p<0.001$). When compared to their female counterparts, male patients were more likely to receive a first-generation antipsychotic (31.6% vs. 28.2%), clozapine (0.8% vs. 0.3%) or olanzapine (22.4% vs. 21.2%). In contrast,

risperidone and quetiapine use were more common in women than men (43.5% vs. 39.9%, and 6.9% vs. 5.3%, respectively).

H_{1b}: Rejected.

3.1.3.2.3 Use of Specific Antipsychotic Agents According to Race/Ethnicity

H_{1c}: The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient race/ethnicity.

The use of the various antipsychotic agents differed significantly when stratified according to patient race/ethnicity ($\chi^2 = 160.710$, $df=12$, $p<0.001$). Blacks were less likely to receive olanzapine or risperidone, and more likely to receive a first-generation antipsychotic when compared to the other racial/ethnic groups (Table 3.11). Conversely, Hispanic patients were more likely to receive risperidone, and less likely to receive a first-generation antipsychotic.

H_{1c}: Rejected.

Table 3.11: Distribution of Index Antipsychotic Agent for Texas Medicaid and when Stratified According to Age, Gender, Race/Ethnicity and Primary Mental Health Diagnosis

Stratifications	Index Antipsychotic Agent (%) ¹				
	FGA	Clozapine ²	Olanzapine	Quetiapine	Risperidone
Overall ³	29.3	0.5	21.6	6.3	42.2
Age (years)					
18-34	29.2	1.7	16.7	6.3	46.1
35-44	33.0	0.8	25.4	6.3	34.6
45-54	33.6	0.4	23.9	6.2	35.8
55-64	30.6	0.3	22.1	6.6	40.4
≥ 65	26.7	0.1	18.7	6.3	48.3
Gender					
Male	31.6	0.8	22.4	5.3	39.9
Female	28.2	0.3	21.2	6.9	43.5
Race/Ethnicity ⁴					
White	27.7	0.5	21.9	7.3	42.7
Black	35.4	0.3	20.6	5.2	38.5
Hispanic	26.4	0.3	21.6	5.0	46.7
Other	30.9	1.2	22.7	5.7	39.4
Primary Mental Health Diagnosis ⁵					
Schizophrenia	36.5	2.4	26.1	4.5	30.5
Bipolar Disorder	22.1	0.3	27.7	8.5	41.4
Dementia	20.9	0.0	21.5	7.5	50.1
Psychotic Disorder	27.4	0.0	18.8	7.5	46.3
Non-Psychotic Disorder	25.0	0.0	21.4	8.7	44.8
No Mental Health Diagnosis	35.1	0.2	17.3	4.6	42.8

^{1.} Age Strata: $\chi^2=416.748$, df=16, p<0.001; Gender: $\chi^2=76.901$, df=4, p<0.001; Race/Ethnicity: $\chi^2=160.710$, df=12, p<0.001; Primary Mental Health Diagnosis: $\chi^2=845.046$, df=20, p<0.001.

^{2.} N=93.

^{3.} N=19,430 for all comparisons except Primary Mental Health Diagnosis (N=17,230).

^{4.} ‘Other’ category comprised of Native American, Asian American and Others.

^{5.} N= 17,230 (Patients with mental retardation (N=2,200) excluded).

3.1.3.2.4 Use of Antipsychotic Agents According to Primary Mental Health Diagnosis

H_{1d}: The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient primary mental health diagnosis.

After excluding patients with a diagnosis of mental retardation (N=2,200) because of the unreliability of other mental health diagnoses in this group, Chi-square analysis indicated a significant relationship between choice of antipsychotic agent and primary mental health diagnosis ($\chi^2 = 845.046$, df=20, $p < 0.001$). Clozapine and the first-generation antipsychotics were more likely to be used in patients with schizophrenia, whereas olanzapine was more likely to be used in patients with bipolar disorder (Table 3.11). While risperidone was used as index therapy in 42.2 percent of the overall population, the use of this agent varied from 30.5 percent in patients with schizophrenia, to 50.1 percent in patients with dementia (Table 3.11).

H_{1d}: **Rejected.**

3.1.3.3 Antipsychotic Medication: Dose of Second-Generation Antipsychotic Agents (Objective 2)

As outlined in section 2.4.2.3.3 (Chapter 2), the dose for each second-generation antipsychotic agent was inferred from the information available on the quantity, strength and number of days supplied for each prescription. The mean daily treatment dose was calculated for each patient from their index date to their study endpoint date. The calculated doses were examined for appropriateness based on the dose ranges outlined in Table 2.2, and outliers excluded accordingly. Table 3.12 illustrates the average treatment doses for the second-

generation antipsychotics. As these were not normally distributed (positively skewed), both mean and median daily doses are reported.

As a form of sensitivity analysis, two additional dose calculation methods were examined. In the first, mean daily treatment doses were calculated from the index date to the study endpoint date for each patient but gaps in patient therapy (which were presumably due to non-adherence) were excluded. Secondly, the dose a patient was receiving on the day they experienced their study endpoint was also examined. For each agent, while the calculated doses in both of these methods were slightly higher than those reported in Table 3.12, they did not differ clinically. For example, the mean daily dose for risperidone excluding gaps in therapy was 1.87mg (SD: 1.67) with a median of 1.12mg; the mean dose on the day of the study endpoint was 1.91mg (SD: 2.15), with a median of 1.00mg; as compared to 1.82mg (SD: 1.67) and a median of 1.09 reported in Table 3.12. The average daily doses reported in Table 3.12 were, therefore, assumed to be a reliable estimate of patient's antipsychotic dose for this study.

Table 3.12: Average Daily Dose (Milligrams) for the Second-Generation Antipsychotics in the Texas Medicaid Study Population

Agent	N ¹	Mean (SD)	Median
Clozapine	91	426.21 (289.54)	400.00
Olanzapine	4,191	8.21 (5.80)	5.77
Quetiapine	1,228	128.09 (138.03)	75.00
Risperidone	8,197	1.82 (1.67)	1.09

¹. N=24 dose outliers excluded (N=2: clozapine; N=8: olanzapine; N=3: quetiapine; N=11: risperidone).

To allow for dose-based comparisons between the second-generation antipsychotic agents, patients were classified as receiving 'Low,' 'Medium, or 'High' dose antipsychotic therapy based on the mean daily dose of antipsychotic

they received. These strata were based on therapeutic efficacy as discussed in Chapter 2, section 2.4.2.3.3. Because of concerns that these dose strata may not be relevant for elderly patients due to differences in treatment tolerability and effect, a modified dose stratification was proposed for patients aged 65 years or older. The results of these classifications are illustrated in Table 3.13. Using the standard dose classification, the majority of patients were identified as receiving a low dose of antipsychotic. Using the revised stratification scheme for patients aged 65 years or older, 36.7 percent of patients were classified as taking a low dose, with 17.7 percent regarded as taking a high dose.

Table 3.13: Classification of Mean Daily Antipsychotic Dose as ‘Low,’ ‘Medium’ or ‘High’ Dose for All Patients, by Agent, and by Age < 65 or ≥65 years for the Texas Medicaid Study Population

Stratification	N (%)		
	Low Dose	Medium Dose	High Dose
All Patients^{1,2}	10,444 (76.6)	2,426 (17.8)	746 (5.5)
By Agent			
Olanzapine	3,211 (76.6)	484 (11.5)	496 (11.8)
Quetiapine	1,115 (90.8)	92 (7.5)	21 (1.7)
Risperidone	6,118 (74.6)	1850 (22.6)	229 (2.8)
By Age Group			
Patients < 65 Years ^{2,3}	4,292 (62.6)	1,870 (27.3)	686 (10.0)
Patients ≥ 65 Years ^{4,5}	2,488 (36.7)	3,083 (45.5)	1,197 (17.7)

^{1.} N = 13,616 (Dose outliers (N=22) and patients treated with clozapine (N=93) omitted).

^{2.} Mean Daily Dose Reference Ranges: Olanzapine - Low: ≤ 10mg; Medium: >10mg to ≤ 15mg; High: >15mg; Quetiapine - Low: ≤ 300mg; Medium: >300mg to ≤ 600mg; High: >600mg; Risperidone - Low: ≤ 2mg; Medium: >2mg to ≤ 6mg; High: >6mg.

^{3.} N = 6,848 (Dose outliers (N=13) and patients treated with clozapine (N=74) omitted).

^{4.} N = 6,768 (Dose outliers (N=9) and patients treated with clozapine (N=19) omitted).

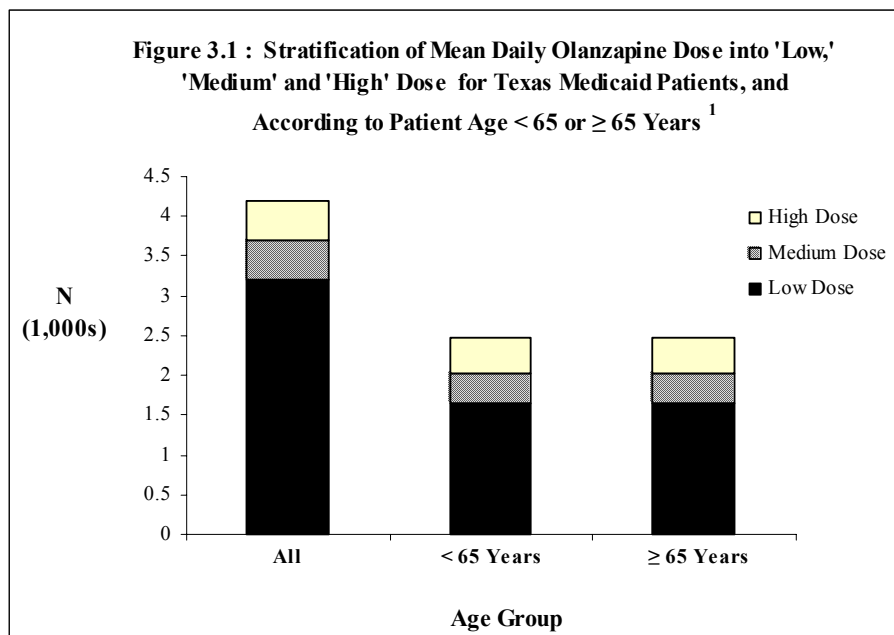
^{5.} Mean Daily Dose Reference Ranges: Olanzapine - Low: ≤ 5mg; Medium: >5mg to ≤ 10mg; High: >10mg; Quetiapine - Low: ≤ 100mg; Medium: >100mg to ≤ 300mg; High: >300mg; Risperidone - Low: ≤ 0.5mg; Medium: >0.5mg to ≤ 1.5mg; High: >1.5mg.

3.1.3.3.1 Dose Classification according to Agent

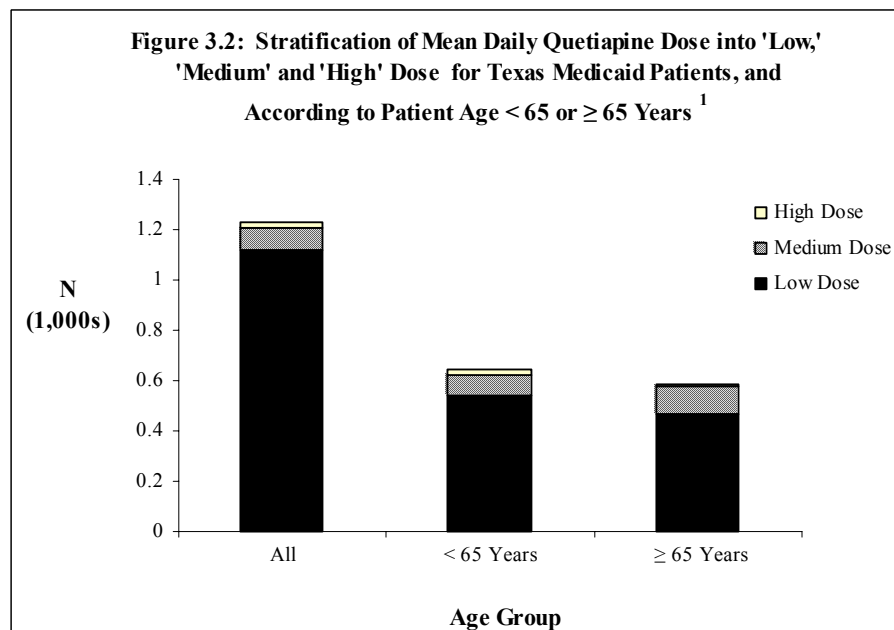
H_{2a}: The classification of mean daily antipsychotic dose as ‘Low,’ ‘Medium,’ or ‘High’ dose will not differ significantly when stratified according to the second-generation agent used.

Table 3.13 and Figures 3.1 to 3.3 illustrate the stratification of patients according to antipsychotic dose range for patients treated with olanzapine, quetiapine or risperidone. For each of the three agents, the majority were categorized as taking low-dose therapy when examined without regard to patient age. Patients taking olanzapine were most likely to receive high-dose therapy (11.8% vs. 1.7% and 2.8% for quetiapine and risperidone, respectively). This difference between agents was significant when examined using chi-square analysis ($\chi^2=754.098$, $df=4$, $p<0.001$). A similar trend in distribution was noted for patients aged less than 65 years. Using the modified dose stratification system for patients aged 65 years or older resulted in a similar distribution of patients into ‘Low,’ ‘Medium,’ or ‘High’ dose for those treated with olanzapine and quetiapine. A difference was noted for patients aged 65 years or older treated with risperidone; however, under the modified dose stratification, the majority of these patients (56.5%) were classified as receiving medium-dose therapy and only 20.2 percent classified as receiving low-dose therapy (Figure 3.3).

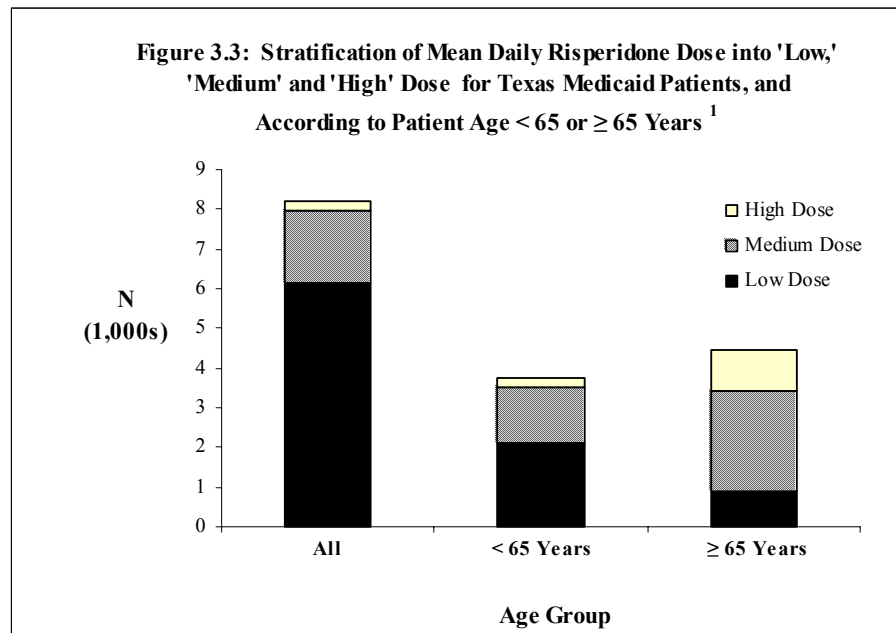
H_{2a}: Rejected.



1. Dose Reference Ranges for 'All' patients and '< 65 years': - 'Low': ≤ 10mg; 'Medium' : >10mg to ≤ 15mg; 'High' : >15mg; Patients '≥65 years': 'Low': ≤ 5mg; 'Medium' : >5mg to ≤ 10mg; 'High' : >10mg.



1. Dose Reference Ranges for 'All' patients and '<65 years': - 'Low': ≤ 300mg; 'Medium' : >300mg to ≤ 600mg; 'High' : >600mg; Patients '≥65 years': 'Low': ≤ 100mg; 'Medium' : >100mg to ≤ 300mg; 'High' : >300mg.



¹. Dose Reference Ranges for 'All' patients and '<65 years': - 'Low': ≤ 2mg; 'Medium' : >2mg to ≤ 6mg; 'High' : >6mg; Patients '≥65 years': 'Low': ≤ 0.5mg; 'Medium' : >0.5mg to ≤ 1.5mg; 'High' : >1.5mg.

3.1.3.3.2 Dose of Second-Generation Antipsychotic Agents According to Patient Age

For each of the second-generation agents, olanzapine, quetiapine and risperidone, the mean daily dose use was examined according to patient age (Table 3.14). Hypotheses 2b and 2f relating to clozapine and ziprasidone were not tested due to the inadequate sample sizes.

H_{2c-e}: The mean daily antipsychotic dose for the second-generation antipsychotics (olanzapine, quetiapine, risperidone) will not differ when stratified according to patient age.

ANOVA and Kruskal-Wallis tests revealed significant differences (p<0.001) in the mean daily dose for all three agents according to patient age (Table 3.14). For each agent, the mean daily dose was highest for patients aged

44 years or younger, decreasing thereafter with increasing patient age. Post-hoc analyses for both risperidone and olanzapine showed significant differences between patients aged 55 to 64 years, and those 65 years or older, when compared to each other ($p \leq 0.002$), to patients aged less than 35 years, between 35 and 44 years, and those aged between 45 and 54 years. A similar pattern was evident for quetiapine, with the exception that the mean daily dose for patients aged 55 to 64 years did not differ significantly from that for patients aged 45 to 54 years ($p = 0.073$).

H_{2c}: Rejected (Olanzapine).

H_{2d}: Rejected (Quetiapine).

H_{2e}: Rejected (Risperidone).

Table 3.14: Mean Daily Dose (Milligrams) of the Second-Generation Antipsychotic Agents for Texas Medicaid Enrollees and when Stratified According to Age and Primary Mental Health Diagnosis

Stratifications	Mean Daily Dose (SD)		
	Olanzapine	Quetiapine	Risperidone
Overall⁴	8.21 (5.87)	124.39 (136.77)	1.80 (1.70)
Age (years)			
18-34	10.82 (6.18)	205.39 (191.29)	2.87 (2.15)
35-44	11.19 (6.52)	183.22 (160.11)	2.99 (2.27)
45-54	10.42 (6.40)	176.85 (167.57)	2.81 (2.11)
55-64	8.91 (5.32)	124.32 (141.73)	2.15 (1.82)
≥ 65	5.39 (3.76)	76.50 (70.43)	1.19 (0.94)
<i>ANOVA</i>	<i>p<0.001¹</i>	<i>p<0.001²</i>	<i>p<0.001³</i>
Primary Mental Health Diagnosis			
Schizophrenia	12.04 (6.73)	273.16 (203.86)	3.55 (2.37)
Bipolar Disorder	8.91 (5.78)	146.33 (149.29)	2.05 (1.76)
Dementia	4.87 (3.00)	79.59 (82.57)	1.12 (0.85)
Psychotic Disorder	6.13 (4.38)	85.36 (75.69)	1.34 (1.05)
Non-Psychotic Disorder	6.77 (4.61)	95.51 (93.60)	1.57 (1.44)
No Mental Health Diagnosis	7.92 (5.70)	102.56 (108.37)	1.63 (1.52)
<i>ANOVA</i>	<i>p<0.001¹</i>	<i>p<0.001²</i>	<i>p<0.001³</i>

- ¹. Olanzapine (N=3,731 excluding outliers and patients with mental retardation): Age strata: F =231.437, df=4, p<0.001; Primary Mental Health Diagnosis: F = 132.517, df=5, p<0.001.
- ². Quetiapine (N=1,106 excluding outliers and patients with mental retardation): Age strata: F =48.910, df=4, p<0.001; Primary Mental Health Diagnosis: F=49.085, df=5, p<0.001.
- ³. Risperidone (N=7,258 excluding outliers and patients with mental retardation): Age strata: F =483.399, df=4, p<0.001; Primary Mental Health Diagnosis: F=294.518, df=5, p<0.001.
- ⁴. N= 12,095 (N=1,543 patients with mental retardation and dose outliers excluded).

3.1.3.3.3 Dose of Second-Generation Antipsychotic Agents According to Primary Mental Health Diagnosis

The mean daily doses for olanzapine, quetiapine and risperidone were examined according to the primary mental diagnosis for which they were presumed to be prescribed (Table 3.14). Hypotheses 2g and 2k relating to clozapine and ziprasidone were not tested due to inadequate sample size. Patients with a diagnosis of mental retardation were excluded from this analysis due to the difficulty of making other mental health diagnoses in this population.

H_{2h-j}: The mean daily antipsychotic dose for the second-generation antipsychotics (olanzapine, quetiapine, risperidone) will not differ significantly when stratified according to the primary mental health diagnosis.

Regardless of agent, when examined using ANOVA and Kruskal-Wallis tests, the mean daily treatment dose differed significantly ($p < 0.001$) according to the presumed treatment indication (Table 3.14). A similar dosing pattern was seen for the three agents, with the highest doses prescribed for patients with schizophrenia, decreasing in the following order: bipolar disorder; no mental health diagnosis; non-psychotic disorder; psychotic disorder; with the lowest doses prescribed for patients with dementia (Table 3.14). Doses for schizophrenia ranged from 26 to 46 percent higher than those prescribed for bipolar disorder, and were approximately 60 to 70 percent higher than those prescribed for patients with dementia (Table 3.14). Post-hoc analysis for olanzapine and risperidone were significant ($p \leq 0.007$ and $p \leq 0.002$, respectively) for all comparisons, with the exception of doses prescribed to patients with a non-psychotic disorder compared to those without a mental health diagnosis ($p = 0.410$ and $p = 0.848$, respectively). In contrast, whereas the doses of quetiapine

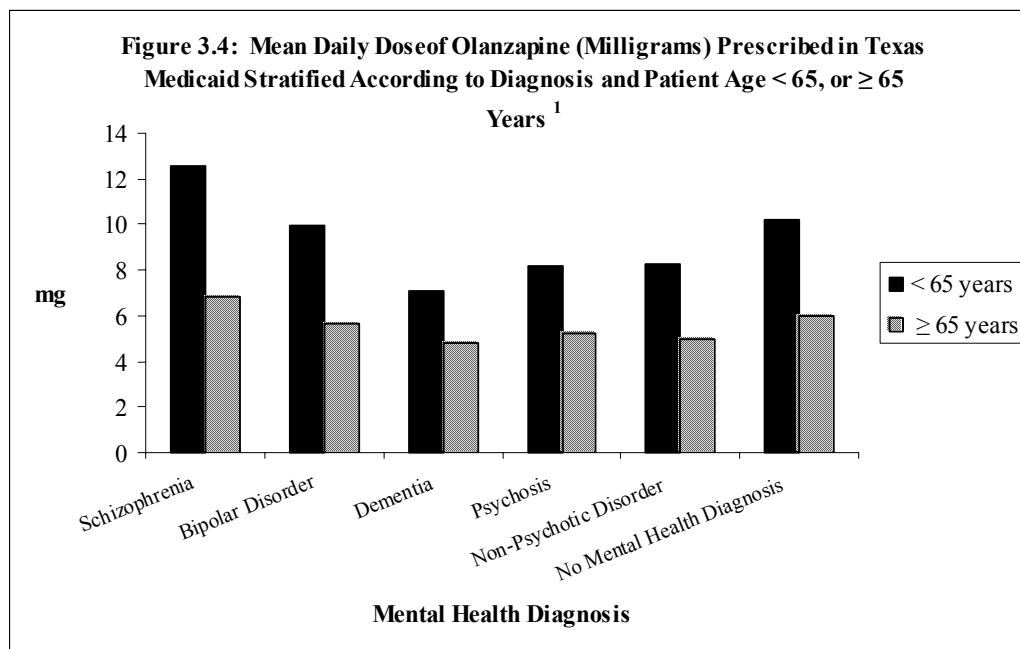
prescribed for schizophrenia and bipolar disorder differed significantly from each other, and from those used for each of the other diagnoses, no other comparisons between treatment indications were significantly different for this agent.

H_{2h}: Rejected (Olanzapine).

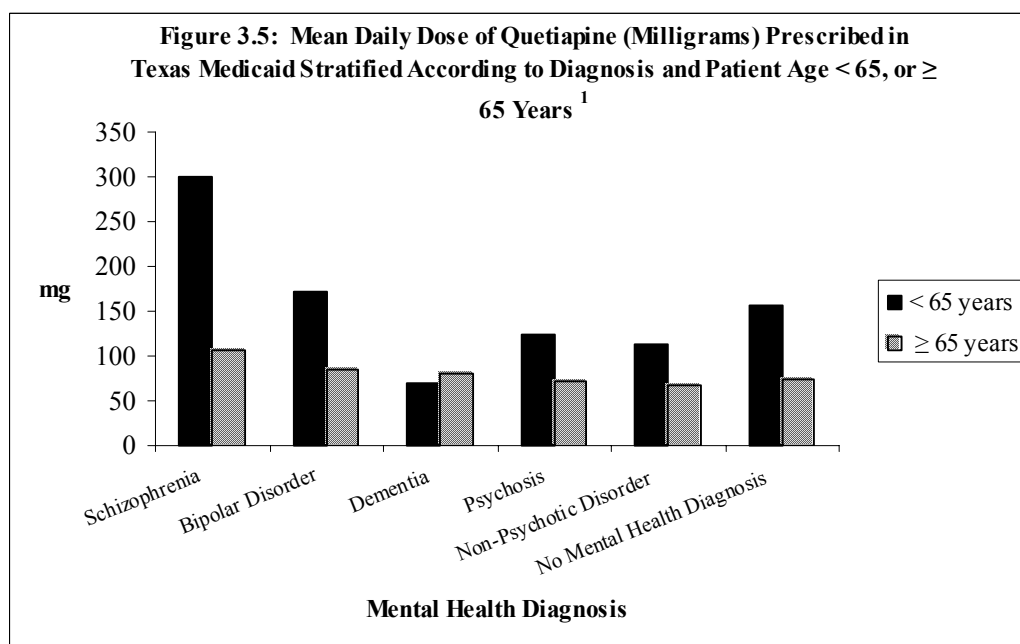
H_{2i}: Rejected (Quetiapine).

H_{2j}: Rejected (Risperidone).

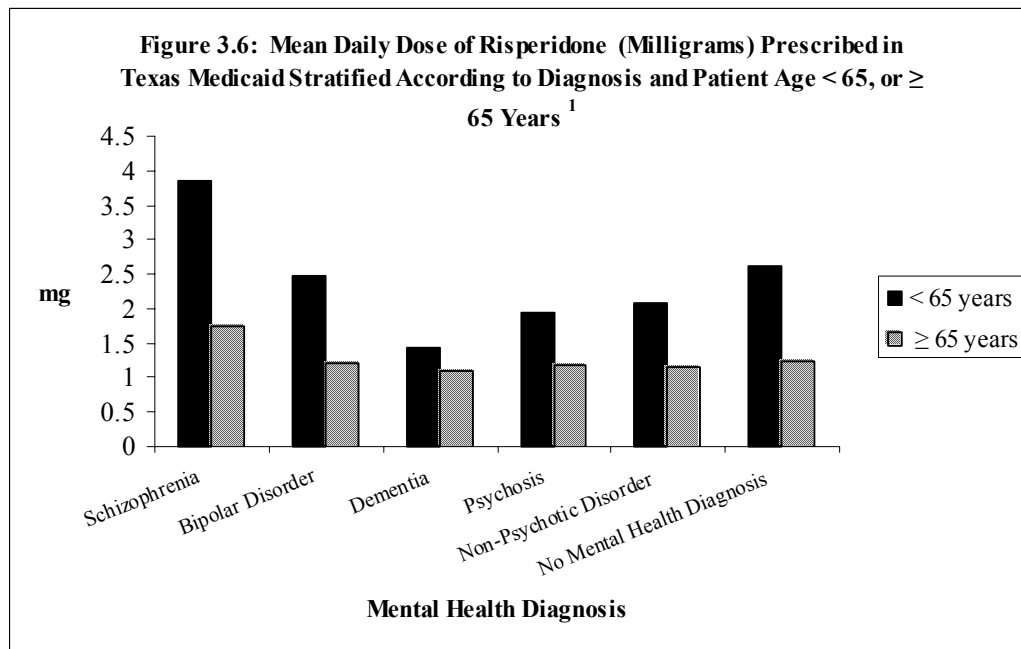
Initial analyses showed a difference in antipsychotic dose according to both patient age and treatment indication. Additional bivariate analyses were conducted to further examine the pattern of prescribing after stratifying the population into those less than 65 years, and those aged 65 years or older. Figures 3.4 to 3.6 illustrate the mean daily doses for olanzapine, quetiapine and risperidone according to treatment indication and within these age strata. With the exception of quetiapine prescribing in patients aged 65 years or older, ANOVA revealed that the dose of antipsychotic varied significantly according to treatment indication ($p < 0.001$) in both age strata. Regardless of the antipsychotic agent, when compared to patients aged less than 65 years, older patients received approximately 50 percent of the dose prescribed to their younger counterparts (range: 43.4% to 51.2%). Consistent with previous findings, the mean daily dose was highest for patients with a diagnosis of schizophrenia regardless of agent or age group. With the exception of quetiapine prescribing in patients aged 65 years or older, the lowest mean daily dose of antipsychotic was prescribed to patients with a diagnosis of dementia.



¹. N=3,731.



¹. N=1,106.



¹. N=7,258.

3.1.3.4 Antipsychotic Medication: Duration of Antipsychotic Therapy (Objective 2)

The duration of antipsychotic treatment was inferred from the number of days of medication supplied to a patient from their index date until a study endpoint occurred, with a maximum period of follow-up of 365 days. Treatment was assumed to have been discontinued if a prescription refill did not occur within the time covered by the existing prescription plus a 50 percent grace-period (e.g., refill within 45 days of a 30-day prescription being dispensed). The mean duration of antipsychotic treatment was 115.2 days (SD: 118.5), with treatment ranging in duration from one to 365 days. Table 3.15 describes the average duration of antipsychotic therapy stratified according to the index antipsychotic agent.

On average, patients remained on treatment longer on the second-generation antipsychotics than the first-generation agents (128.4 days (SD: 123.3) versus 83.3 days (SD: 99.2). This difference was significant ($p < 0.001$) for both the Student T-test and the Mann Whitney test. Within the second-generation agents, the duration of treatment was longest for quetiapine (135.0 days (SD: 126.6)) and shortest for clozapine (80.8 days (SD: 102.7)). After excluding patients treated with clozapine from the analysis due to the small sample size, ANOVA and Kruskal-Wallis tests indicated the difference between the second-generation agents to be significant ($p < 0.001$). A subsequent post-hoc analysis revealed significant differences in the duration of treatment with olanzapine or quetiapine compared to risperidone ($p \leq 0.032$), but not between olanzapine and quetiapine ($p = 0.946$).

Table 3.15: Average Duration of Antipsychotic Therapy (Days) for the Texas Medicaid Study Population Stratified According to the Index Antipsychotic Agent

Antipsychotic Agent	Mean (SD)	Median
First-Generation Agent¹	83.3 (99.2)	31.0
Second-Generation Agent²	128.4 (123.3)	68.0
Clozapine	80.8 (102.7)	30.0
Olanzapine	133.7 (125.0)	75.0
Quetiapine	135.0 (126.6)	77.0
Risperidone	125.3 (121.8)	65.0
All	115.2 (118.5)	60.0

¹. First-generation agents included: Chlorpromazine; Fluphenazine; Haloperidol; Loxapine; Mesoridazine; Molindone; Perphenazine; Pimozide; Thioridazine; Thiothixene and Trifluoperazine.

². No patient received Ziprasidone as their index antipsychotic agent.

3.1.3.5 Antipsychotic Medication: Compliance (Objective 2)

Two components of medication compliance were assessed in this study: adherence and persistence. In order to obtain stable estimates, compliance was assessed only for patients who obtained at least one prescription refill. When records indicated that two or more prescriptions for the same strength of an agent were dispensed on the same day, an assumption was made that an order-entry error had occurred and that invalid entries had not been reversed. These extra prescriptions were omitted from calculations, with only the last prescription entry for that day arbitrarily selected to calculate compliance measures. Adherence was assessed by means of the medication possession ratio (MPR), which reflects the number of days a patient was in possession of their medication. The prescription records of patients with an MPR in excess of 1.5 were evaluated for appropriateness. As outlined in section 2.4.1.1 (Chapter 2), the follow-up period varied for each patient and consisted of the time from the index prescription to the development of a study endpoint (development of diabetes; switching to, or the addition of another antipsychotic agent; absence of any further prescriptions for the agent, or end of follow-up data). The maximum period of follow-up was 365 days. As a form of sensitivity analysis, adherence was also calculated using an intent-to-treat approach, whereby it was measured over a 365-day period for all patients filling more than one antipsychotic prescription (Figure 2.3, Chapter 2).

Persistence was defined as the number of days of continuous therapy during the 365-day follow-up period. Patients refilling their prescription within a 50 percent grace-period were considered to be persistent (e.g., refill within 45 days (30×1.5) of a 30-day prescription being dispensed) with therapy. Persistence with therapy and duration of therapy were synonymous terms, with

the exception that persistence was calculated only for patients filling more than one antipsychotic prescription.

The mean adherence to antipsychotic therapy for the Medicaid population was 0.803 (SD: 0.266) (Table 3.16). When examined over a 365-day period for all patients, a mean adherence rate of 0.600 (SD: 0.316) was noted (Table 3.16). Persistence to antipsychotic therapy varied widely in the study population. As the data were not normally distributed (positive skew) both mean and median values are reported in Table 3.16. The mean persistence with therapy was 128.7 days (SD: 120.2) with a median value of 77.0 days (range: 1 to 365 days).

Table 3.16: Compliance with Antipsychotic Therapy for the Texas Medicaid Study Population as Reflected by Adherence (Medication Possession Ratio) and Persistence (Days) Measures¹

Compliance Measure	Mean (SD)	Median
Adherence		
MPR ²	0.803 (0.266)	0.875
MPR_365 days ³	0.600 (0.316)	0.605
Persistence		
Number of Persistent Days	128.74 (120.24)	77.00

^{1.} N=15,098 (N=4,332 excluded as only one prescription filled in 365-day follow-up period).

^{2.} Adherence calculated until the patient developed diabetes, switched or added an antipsychotic, or had no further refills for the agent within the 365-day follow-up period.

^{3.} Adherence calculated over 365 days for all patients

In addition to calculating mean MPR rates, patients were also categorized according to their level of adherence as outlined in Chapter 2, section 2.4.1.1. As evident in Table 3.17, approximately 40 percent of patients were found to adhere poorly to their antipsychotic therapy, as indicated by MPR rates of less than 0.8. The percentage of patients who filled their prescriptions more frequently than appeared necessary (MPR > 1.1) was 6.2 percent. Using the intent-to-treat

approach (MPR_365 days), 34.6 percent of Texas Medicaid enrollees were categorized as being adherent (MPR_365 days \geq 0.8) with therapy (Table 3.17).

Table 3.17: Frequency Distribution of Adherence to Antipsychotic Therapy as Measured by Medication Possession Ratios (MPR) for the Texas Medicaid Study Population ¹

Antipsychotic Therapy Adherence	N (%)²
MPR³	
0.00 to <0.50 (Non-Adherent)	2,325 (15.4)
0.50 to <0.80 (Partially Adherent)	3,792 (25.1)
0.80 to 1.10 (Adherent)	8,038 (53.2)
>1.10 (Excess Medication Filler)	943 (6.2)
Total	15,098 (99.9)
MPR_365 days⁴	
0.00 to <0.50 (Non-Adherent)	6,349 (42.1)
0.50 to <0.80 (Partially Adherent)	3,519 (23.3)
0.80 to 1.10 (Adherent)	4,956 (32.8)
>1.10 (Excess Medication Filler)	274 (1.8)
Total	15,098 (100.0)

¹. N=4,332 excluded as only one prescription filled in 365-day follow-up period.

². Percentage does not add to 100 due to rounding.

³ MPR calculated until a study endpoint occurred (development of diabetes, addition of an antipsychotic, switching of an antipsychotic), no further prescriptions for the agent were redeemed, or a maximum of 365 days of follow-up.

⁴ MPR_365 days based on the number of days of medication available to a patient during 365 days of follow-up.

3.1.3.5.1 Compliance According to Patient Age

As noted, two measures of compliance with antipsychotic therapy were used in this study: adherence and persistence. The impact of patient age on these outcomes is reported here.

H_{3a}: Adherence with antipsychotic therapy will not differ significantly when stratified according to patient age.

Adherence to therapy differed significantly ($p < 0.001$) according to patient age, with the highest adherence rates documented in patients aged 65 years or older, and the lowest rates documented in patients aged between 35 and 44 years (Table 3.18). Post-hoc analyses revealed significant differences between those aged 65 years or older, compared with all other age strata ($p < 0.001$), and between those aged between 35 and 44 years and all other strata ($p \leq 0.003$). When adherence was assessed over 365 days (MPR_365 days), a similar trend in adherence according to patient age was noted.

H_{3a}: Rejected.

H_{3b}: Persistence with antipsychotic therapy will not differ significantly when stratified according to patient age.

Persistence with antipsychotic therapy was noted to differ according to patient age (Table 3.18). Persistence was highest for patients aged 65 years and older, and lowest for patients aged between 35 and 44 years. The variation in persistence with patient age was significant when analyzed using ANOVA and Kruskal-Wallis tests ($p < 0.001$). Post-hoc analyses revealed that patients aged 65 years or older had significantly higher persistence levels compared with all other age-strata ($p \leq 0.029$). The only other significant comparison was for patients aged

between 18 and 34 years, who were significantly more persistent with therapy compared to those aged between 35 and 44 years ($p=0.015$).

H_{3b}: **Rejected.**

Table 3.18: Adherence to Antipsychotic Therapy for Texas Medicaid Patients Stratified According to Age, Gender, Race/Ethnicity, Primary Mental Health Diagnosis and Index Antipsychotic Agent

Stratification	N	Adherence (MPR) ¹ Mean (SD)	Adherence (MPR_365 days) ² Mean (SD)	Persistence (Days) ³ Mean (SD)
All	15,098	0.803 (2.66)	0.600 (0.316)	128.7 (120.2)
Age (years)				
18-34	2,192	0.778 (0.256)	0.587 (0.309)	125.8 (117.6)
35-44	2,338	0.744 (0.273)	0.566 (0.305)	115.0 (114.0)
45-54	2,081	0.773 (0.263)	0.590 (0.308)	122.9 (116.7)
55-64	1,207	0.794 (0.263)	0.603 (0.311)	125.5 (116.6)
≥ 65	7,280	0.838 (0.264)	0.617 (0.323)	136.2 (124.0)
<i>ANOVA</i>		<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>
Gender				
Male	5,291	0.791 (0.269)	0.605 (0.316)	128.1 (120.7)
Female	9,807	0.808 (0.264)	0.597 (0.316)	129.1 (120.0)
<i>Student T-test</i>		<i>p<0.001</i>	<i>p=0.141</i>	<i>p=0.653</i>
Race/Ethnicity⁴				
White	8,545	0.831 (0.259)	0.628 (0.319)	139.3 (124.9)
Black	3,124	0.756 (0.275)	0.558 (0.307)	111.8 (111.3)
Hispanic	2,359	0.774 (0.269)	0.559 (0.308)	115.5 (111.6)
Other	1,070	0.774 (0.257)	0.586 (0.306)	122.9 (117.1)
<i>ANOVA</i>		<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>

Table 3.18 (cont): Adherence to Antipsychotic Therapy for Texas Medicaid Patients Stratified According to Age, Gender, Race/Ethnicity, Primary Mental Health Diagnosis and Index Antipsychotic Agent

Stratification	N	Adherence (MPR) Mean (SD)	Adherence (MPR_365 days) Mean (SD)	Persistence (Days) Mean (SD)
Primary Mental Health Diagnosis⁵				
Schizophrenia	2,361	0.761 (0.259)	0.598 (0.297)	118.7 (115.4)
Bipolar Disorder	2,071	0.785 (0.262)	0.570 (0.303)	117.2 (110.1)
Dementia	2,045	0.853 (0.252)	0.628 (0.315)	136.9 (123.8)
Psychotic Disorder	1,089	0.825 (0.267)	0.602 (0.325)	131.0 (121.1)
Non-Psychotic Disorder	1,835	0.807 (0.272)	0.575 (0.322)	124.0 (116.7)
No Mental Health Diagnosis	3,923	0.798 (0.274)	0.592 (0.327)	130.1 (123.1)
<i>ANOVA</i>		<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>
Antipsychotic Agent⁶				
First-Generation Agent ⁷	15,012			
Olanzapine	4,065	0.723 (0.299)	0.494 (0.309)	96.2 (103.7)
Quetiapine	3,437	0.833 (0.241)	0.642 (0.307)	144.8 (125.2)
Risperidone	954	0.854 (0.235)	0.685 (0.310)	149.8 (126.6)
	6,556	0.828 (0.251)	0.630 (0.311)	138.1 (122.4)
<i>ANOVA</i>		<i>p<0.001</i>	<i>p<0.001</i>	<i>p<0.001</i>

- ^{1.} Adherence (MPR): Age strata: $F=73.175$, $df=4$, $p<0.001$; Gender: $t=-3.688$, $df=10675.3$, $p<0.001$; Race/Ethnicity: $F=77.829$, $df=3$, $p<0.001$; Primary Mental Health Diagnosis: $F=30.023$, $df=5$, $p<0.001$; Antipsychotic Agent: $F=173.120$, $df=3$, $p<0.001$.
- ^{2.} Adherence (MPR_365 days): Age strata: $F=13.258$, $df=4$, $p<0.001$; Gender: $t=1.472$, $df=15,096$, $p=0.141$; Race/Ethnicity: $F=54.001$, $df=3$, $p<0.001$; Primary Mental Health Diagnosis: $F=8.691$, $df=5$, $p<0.001$; Antipsychotic Agent: $F=225.643$, $df=3$, $p<0.001$.
- ^{3.} Persistence: Age strata: $F=16.419$, $df=4$, $p<0.001$; Gender: $t=-0.450$, $df=15,096$, $p=0.653$; Race/Ethnicity: $F=53.613$, $df=3$, $p<0.001$; Primary Mental Health Diagnosis: $F=6.704$, $df=5$, $p<0.001$; Antipsychotic Agent: $F=146.6$, $df=3$, $p<0.001$.
- ^{4.} 'Other' category comprised of Asian American, Native American and 'Other' racial/ethnic groups.
- ^{5.} Patients with Mental Retardation ($N=1,784$) excluded.
- ^{6.} Patients treated with Clozapine ($N=86$) excluded due to small sample size.
- ^{7.} First-generation agents included: Chlorpromazine; Fluphenazine; Haloperidol; Loxapine; Mesoridazine; Molindone; Perphenazine; Pimozide; Thioridazine; Thiothixene and Trifluoperazine.

3.1.3.5.2 Compliance According to Patient Gender

The effect of patient gender on the two measures of compliance with antipsychotic therapy examined in this study (adherence and persistence) is reported here.

H_{3c}: Adherence with antipsychotic therapy will not differ significantly when stratified according to patient gender.

Women were found to be significantly more adherent to therapy than men ($p < 0.001$ for Student t-test and the Mann Whitney test) with a mean adherence rate of 0.808 (SD: 0.264) compared to 0.791 (SD: 0.269) for men (Table 3.18). The results from the sensitivity analysis comparing adherence over 365 days for men and women did not confirm this finding, with no difference in adherence based on patient gender noted ($p = 0.141$ for Student t-test, and $p = 0.164$ for the Mann Whitney test).

H_{3c}: Rejected.

H_{3c}: Persistence with antipsychotic therapy will not differ significantly when stratified according to patient gender.

No difference in persistence levels were found between women and men, with mean levels of 129.1 and 128.1 days, respectively, noted (Table 3.18).

H_{3d}: Accepted.

3.1.3.5.3 Compliance According to Patient Race/Ethnicity

As before, in testing these hypotheses, adherence and persistence were used as measures of compliance with antipsychotic therapy.

H_{3e}: Adherence with antipsychotic therapy will not differ significantly when stratified according to patient race/ethnicity.

Adherence to therapy differed significantly ($p < 0.001$) according to patient race/ethnicity when examined using ANOVA and Kruskal-Wallis tests, with the highest adherence rates documented for Whites, and the lowest rates documented for Black patients (Table 3.18). Post-hoc analyses revealed significant differences between Whites compared with any minority group ($p < 0.001$). The results from the sensitivity analysis examining adherence over 365 days were consistent with these findings, with the exception that the comparison between Black patients and those in the 'Other' group also differed significantly ($p \leq 0.046$).

H_{3e}: Rejected.

H_{3f}: Persistence with antipsychotic therapy will not differ significantly when stratified according to patient race/ethnicity.

A similar pattern was noted for persistence with antipsychotic therapy (Table 3.18). Persistence was highest for White patients, and lowest for Black patients. The variation in persistence with patient race/ethnicity was significant when analyzed using ANOVA and Kruskal-Wallis tests ($p < 0.001$). Post-hoc analyses revealed that White patients had significantly higher persistence levels compared with all other racial/ethnic groups ($p \leq 0.001$). The only other

significant comparison was for Black patients, who were significantly less persistent with therapy compared to patients in the 'Other' racial /ethnic group ($p=0.035$).

H_{3f}: **Rejected.**

3.1.3.5.4 Compliance According to Primary Mental Health Diagnosis

Patient compliance with antipsychotic therapy, as reflected by adherence and persistence measures, was assessed after stratifying the population according to the primary mental health diagnosis for which antipsychotic therapy was presumed to be prescribed. Patients with a diagnosis of mental retardation were excluded from this analysis due to the difficulty of making other mental health diagnoses in this population.

H_{3g}: Adherence with antipsychotic therapy will not differ significantly when stratified according to primary mental health diagnosis.

Adherence to therapy differed significantly ($p<0.001$) according to mental health diagnosis when examined using ANOVA and Kruskal-Wallis tests, with the highest adherence rates documented for patients with dementia, and the lowest rates documented for patients with schizophrenia (Table 3.18). Post-hoc analyses revealed that patients with schizophrenia had significantly lower adherence rates compared with any other diagnostic group ($p\leq 0.031$). In contrast, patients with dementia had significantly higher adherence rates compared to all other diagnostic groups ($p<0.001$), with the exception of those with a psychotic disorder ($p=0.053$). Other significant contrasts were for patients with bipolar disorder and those with no mental health diagnosis, who had lower adherence rates when compared to those with a psychotic disorder ($p=0.001$ and $p=0.038$, respectively). In the sensitivity analysis examining adherence over 365 days,

adherence varied by diagnosis ($p < 0.001$), and was again noted to be highest for patients with dementia. Using this methodology however, the lowest adherence rates were noted for patients with bipolar disorder (Table 3.18).

H_{3g}: **Rejected.**

H_{3h}: Persistence with antipsychotic therapy will not differ significantly when stratified according to primary mental health diagnosis.

Persistence with antipsychotic therapy was also noted to vary significantly according to mental health diagnosis (Table 3.18) when analyzed using ANOVA and Kruskal-Wallis tests ($p < 0.001$). Persistence was highest for patients with dementia, and lowest for patients with bipolar disorder, with mean numbers of persistent days of 136.9 (SD: 123.8) and 117.2 (SD: 110.1), respectively. Post-hoc analyses revealed significant comparisons in persistence levels for patients with dementia compared to patients with schizophrenia, bipolar disorder and those with non-psychotic disorders ($p \leq 0.011$). The mean number of persistent days for patients with no mental health diagnosis was 130.1 days (SD: 123.1) which was significantly higher than for patients with schizophrenia or bipolar disorder ($p \leq 0.003$). The only other significant contrast was between patients with bipolar disorder compared to those with a psychotic disorder ($p = 0.021$).

H_{3h}: **Rejected.**

3.1.3.5.5 Compliance According to the Antipsychotic Agent Prescribed

After stratifying patients according to their index antipsychotic therapy, compliance with therapy was again assessed using adherence and persistence measures. Patients treated with clozapine (n=93) were excluded from this analysis due to the small sample size. No patient received ziprasidone as their index antipsychotic agent. Patients treated with any first-generation antipsychotic agent were assessed as a single group.

H_{3i}: Adherence with antipsychotic therapy will not differ significantly when stratified according to the specific antipsychotic agent prescribed.

Adherence to therapy was found to differ significantly ($p < 0.001$) according to the specific agent prescribed, when examined using ANOVA and Kruskal-Wallis tests. Adherence rates were noted to decline in the following order: quetiapine, olanzapine, risperidone, first-generation antipsychotic (Table 3.18). Post-hoc analyses revealed that adherence rates were lower for patients treated with a first-generation antipsychotic compared with those treated with any other agent ($p < 0.001$). The only other significant contrast was between quetiapine and risperidone ($p = 0.009$), with mean adherence rates of 0.854 (SD: 0.235) and 0.828 (SD: 0.251), respectively. The results from the sensitivity analysis examining adherence over 365 days (MPR_365 days) confirmed these findings (Table 3.18).

H_{3i} : Rejected.

H_{3j}: Persistence with antipsychotic therapy will not differ significantly when stratified according to the specific antipsychotic agent prescribed.

ANOVA and Kruskal-Wallis tests indicated that persistence with antipsychotic therapy varied significantly ($p < 0.001$) according to the agent prescribed (Table 3.18). Persistence was highest for patients treated with quetiapine, and lowest for patients treated with a first-generation antipsychotic agent, with mean numbers of persistent days of 149.8 (SD: 126.6) and 96.2 (SD: 103.7), respectively. In post-hoc analyses, all comparisons were significant ($p \leq 0.049$), with the exception of that between olanzapine and quetiapine ($p = 0.703$).

H_{3j} : Rejected.

3.2 Phase II: Prevalence of Diabetes

In phase II of this study, the primary dependent variable was the prevalence of diabetes among patients meeting the study inclusion criteria. This variable was defined as detection of a medical claim with an ICD-9 code for diabetes (ICD-9 code: 250.0-250.99) or a pharmacy claim for insulin, an insulin sensitizing or glucose lowering agent within the 180 days preceding the index antipsychotic prescription. Cases of diabetes noted within the first seven days of antipsychotic therapy were also considered to be prevalent cases and were included in this analysis.

3.2.1 Prevalence of Diabetes

The prevalence of diabetes among patients meeting the inclusion criteria for this study was 16.9 percent. Over 97 percent of these cases (N=3,207) were identified in the 180-day period preceding the index antipsychotic prescription, with only 86 patients identified during the first seven days of antipsychotic therapy. As illustrated in Table 3.19, over 85 percent of prevalent cases were detected by a pharmacy claim (N=2,800), whereas nearly 49 percent were detected by a medical claim (1,611).

Table 3.19: Prevalence of Diabetes in the Texas Medicaid Study Population as Detected by Medical and Pharmacy Claims

Classification and Detection Method	N	Percent (%)
No Diabetes Claim	16,137	83.1
Prevalent Diabetes¹	3,293	16.9
Pharmacy Claim only	1,682	8.7
Medical Claim only	493	2.5
Pharmacy and Medical Claim	1,118	5.8
Total	19,430	100.0

¹. Prevalence defined as detection of diabetes in the 180 days preceding, or six days subsequent to the index antipsychotic prescription.

When examined according to patient age, the largest number of prevalent cases was among patients aged 65 years or older, with the lowest number of cases identified among patients aged between 18 and 34 years (Table 3.20). When compared to a population prevalence of 16.9 percent, the prevalence of diabetes increased with increasing age, to a maximum of 25.0 percent among patients aged between 54 and 64 years, declining to 21.6 percent thereafter (Table 3.20). This variation in prevalence was significant when examined using Chi-square analysis ($p < 0.001$). When the population was stratified by gender, significant differences in the prevalence of diabetes were again noticed ($p < 0.001$), with prevalence rates of 13.6 percent and 18.7 percent noted for men and women, respectively (Table 3.20). The prevalence of diabetes also differed according to racial/ethnic group, with the prevalence for Hispanic patients (25.5%) approximately double that for patients in the ‘Other’ racial/ethnic group (12.4%) (Table 3.20). Again, differences in the prevalence of diabetes by racial/ethnic group were significant when examined using Chi-square analysis ($p < 0.001$). The prevalence of diabetes was also examined after stratifying the

population according to their primary mental health diagnosis (Table 3.20). After excluding patients with a diagnosis of mental retardation (N=2,200), the population prevalence of diabetes in the cohort was 18.0 percent. Within the cohort, the prevalence varied from 20.6 percent for patients with a psychotic disorder to 12.4 percent for patients with schizophrenia. The differences between the diagnostic groups was significant when analyzed using Chi-square analysis ($p<0.001$). Finally, the choice of index antipsychotic agent for patients with prevalent diabetes was examined (Table 3.20). Patients prescribed clozapine (N=93) were excluded from this analysis due to the small treatment numbers. The prevalence of diabetes among patients prescribed a first-generation antipsychotic was 14.8 percent compared to 19.0 percent among those prescribed risperidone. Chi-square analysis was significant ($p<0.001$) for comparisons in prevalence of diabetes according to the antipsychotic agent prescribed.

Table 3.20: Prevalence of Diabetes in the Texas Medicaid Study Population and Stratified According to Age, Gender, Race/Ethnicity, Primary Mental Health Diagnosis and Index Antipsychotic Agent

Prevalent Cases¹	N	Percent (%)²	Chi-Square p value
All	3,293	16.9	
Age (years)			<0.001
18-34	123	4.3	
35-44	298	9.7	
45-54	480	17.8	
55-64	305	25.0	
≥ 65	1,997	21.6	
Gender			<0.001
Male	903	13.6	
Female	2,390	18.7	
Race/Ethnicity³			<0.001
White	1,570	14.7	
Black	739	17.8	
Hispanic	813	25.5	
Other	171	12.4	
Primary Mental Health Diagnosis⁴			<0.001
Schizophrenia	353	12.4	
Bipolar Disorder	499	18.6	
Dementia	502	20.4	
Psychotic Disorder	289	20.6	
Non-Psychotic Disorder	480	19.2	
No Mental Health Diagnosis	983	18.4	

Table 3.20 (cont): Prevalence of Diabetes in the Texas Medicaid Study Population and Stratified According to Age, Gender, Race/Ethnicity, Primary Mental Health Diagnosis and Index Antipsychotic Agent

Prevalent Cases ¹	N	Percent (%)	Chi-Square p value
All	3,293	16.9	
Antipsychotic Agent ⁵			<0.001
First-Generation Agent ⁶	842	14.8	
Olanzapine	675	16.1	
Quetiapine	207	16.8	
Risperidone	1,561	19.0	

1. N=19,430.

2. 'Percent' refers to the percentage of prevalent cases within each individual stratum.

3. 'Other' category comprised of Asian American, Native American and 'Other' racial/ethnic groups.

4. Patients with a diagnosis of mental retardation excluded (N=2,200). Adjusted population prevalence of diabetes: 18.0%.

5. Patients treated with Clozapine excluded (N=93). Adjusted population prevalence of diabetes: 17.0%.

6. First-generation agents included: Chlorpromazine; Fluphenazine; Haloperidol; Loxapine; Mesoridazine; Molindone; Perphenazine; Pimozide; Thioridazine; Thiothixene and Trifluoperazine.

3.2.1.1 Prevalence of Diabetes According to Primary Mental Health Diagnosis (Objective 3)

H_{4a}: The prevalence of diabetes will not differ significantly when stratified according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.

As noted previously, the prevalence of diabetes was 18.0 percent for eligible Texas Medicaid patients after excluding those with a diagnosis of mental retardation. Multivariate logistic regression analysis showed that after controlling for differences in other variables, mental health diagnosis was significantly

associated ($p=0.006$) with the prevalence of diabetes (Table 3.21). The odds of prevalent diabetes were increased for patients with a diagnosis of bipolar disorder ($OR=1.268$, 95% $CI=1.085$ to 1.481), a non-psychotic disorder ($OR=1.253$, 95% $CI=1.068$ to 1.470), or no mental health diagnosis ($OR=1.250$, 95% $CI=1.080$ to 1.448) compared to patients with schizophrenia. Patient race/ethnicity was also significantly associated with the prevalence of diabetes ($p<0.001$). Compared to Whites, the odds of prevalent diabetes were 50 percent higher for Blacks ($OR=1.494$, 95% $CI=1.344$ to 1.661) and over two-fold higher for Hispanic patients ($OR=2.106$, 95% $CI=1.898$ to 2.336). Other variables noted to be significantly associated with an increased prevalence of diabetes were increasing patient age ($OR=1.014$, 95% $CI=1.011$ to 1.017), female gender ($OR=1.164$, 95% $CI=1.061$ to 1.276), a diagnosis of hypertension ($OR=1.814$, 95% $CI=1.662$ to 1.980) or dyslipidemia ($OR=2.230$, 95% $CI=1.980$ to 2.511). Of interest, use of a concomitant diabetogenic medication was associated with an 11 percent decrease in the odds of prevalent diabetes ($OR=0.887$, 95% $CI=0.808$ to 0.974).

H_{4a}: **Rejected.**

Table 3.21: Logistic Regression Analysis of the Risk of Prevalent Diabetes in the Texas Medicaid Study Population after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Use of a Concomitant Diabetogenic Medication) Variables^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Intercept	-3.178 (0.096)	1104.907	<0.001*	0.042	
Age	0.014 (0.001)	113.958	<0.001*	1.014	1.011-1.017
Race/Ethnicity⁵		214.252	<0.001*		
Black	0.402 (0.054)	55.386	<0.001*	1.494	1.344-1.661
Hispanic	0.745 (0.053)	197.848	<0.001*	2.106	1.898-2.336
Other ⁶	0.062 (0.092)	0.455	0.500	1.064	0.889-1.273
Gender⁵					
Female	0.152 (0.047)	10.315	0.001*	1.164	1.061-1.276
Primary Mental Health Diagnosis⁵		16.370	0.006*		
Bipolar Disorder	0.237 (0.079)	8.913	0.003*	1.268	1.085-1.481
Dementia	0.081 (0.088)	0.849	0.357	1.084	0.913-1.289
Psychotic Disorder	0.144 (0.096)	2.256	0.133	1.155	0.957-1.393
Non-Psychotic Disorder	0.225 (0.081)	7.670	0.006*	1.253	1.068-1.470
No Mental Health Diagnosis	0.224 (0.075)	8.590	0.003*	1.250	1.080-1.448
Hypertension	0.595 (0.045)	177.670	<0.001*	1.814	1.662-1.980
Dyslipidemia	0.802 (0.061)	174.998	<0.001*	2.230	1.980-2.511
Concomitant Diabetogenic Medication	-0.120 (0.048)	6.351	0.012*	0.887	0.808-0.974

1. Model $\chi^2 = 908.861$, df=13, p<0.001.

2. N=17,230 (N=2,200 patients with Mental Retardation excluded).

3. Abbreviations: SE – Standard Error; OR = Odds Ratio; CI = Confidence Interval.

4. * Indicates statistical significance at p< 0.05.

5. Reference category for each variable: Race/Ethnicity (White); Gender (Male); Primary Mental Health Diagnosis (Schizophrenia).

6. 'Other' category comprised of Native American, Asian American and 'Others.'

3.3 Phase III: Incidence of Diabetes

In phase III, the primary dependent variable was the incidence of diabetes among patients meeting the inclusion criteria for the study. This variable was defined as detection of a medical claim with an ICD-9 code for diabetes (ICD-9 code: 250.0-250.99) or a pharmacy claim for insulin, an insulin sensitizing or glucose lowering agent in the 12 months subsequent to the prescribing of an antipsychotic prescription. The date of first recording of one of these events served as the date of diagnosis of new-onset diabetes, and was used to estimate the duration of time to the development of diabetes. To ensure that only incident cases were included, only cases of diabetes occurring at least seven days subsequent to the index antipsychotic prescription were considered. New cases of diabetes noted in the first 30 days after discontinuation of antipsychotic therapy were also considered to be attributed to that agent.

3.3.1 Incidence of Diabetes

The incidence of diabetes among patients meeting the inclusion criteria for this study was 2.37 percent (N=382) for this Texas Medicaid population. Of these, 44 patients (11.5%) were identified during the 30-day period following the discontinuation of antipsychotic therapy. Over 59 percent (N=226) of new-onset cases were detected by a pharmacy claim, whereas over 75 percent (N=288) were detected by a medical claim (Table 3.22). The mean time to onset of diabetes was 95.9 days (SD: 85.1), with a median time to onset of 62.5 days (range: 7 to 362 days).

Table 3.22: Incidence of Diabetes in the Texas Medicaid Study Population as Detected by Medical and Pharmacy Claims

Classification and Detection Method	N ²	Percent (%)
No Diabetes Claim	15,755	97.63
New-Onset Diabetes¹	382	2.37
Pharmacy Claim only	94	0.58
Medical Claim only	156	0.97
Pharmacy and Medical Claim	132	0.82
Total	16,137	100.0

¹. Incidence defined as detection of diabetes between 7 and 365 days subsequent to the index antipsychotic prescription.

². N=3,293 patients with prevalent diabetes excluded.

When compared to a population incidence of 2.4 percent, the incidence of diabetes increased with increasing age, to a maximum of 3.4 percent among patients aged between 55 and 64 years, declining to 2.8 percent thereafter (Table 3.23). This variation in incidence was significant when examined using Chi-square analysis ($p < 0.001$). When the population was stratified by gender, a significant difference in the incidence of diabetes was again noticed ($p < 0.001$) with incidence rates of 1.7 percent and 2.7 percent noted for men and women, respectively, (Table 3.23). The incidence of diabetes also differed according to racial/ethnic group with the incidence for Hispanic patients double that for patients in the in the ‘Other’ racial/ethnic group (Table 3.23). Again, differences in the incidence of diabetes by racial/ethnic group were significant when examined using Chi-square analysis ($p < 0.001$). The incidence of diabetes was also examined after stratifying the population according to their primary mental health diagnosis (Table 3.23). After excluding patients with a diagnosis of mental retardation (N=2,013), the population incidence of diabetes was 2.6 percent. This varied from 2.0 percent for patients with schizophrenia, to 3.2 percent for

patients with a non-psychotic disorder. This difference between the diagnostic groups was not significant when analyzed using Chi-square analysis ($p=0.051$). Finally, the association between the index antipsychotic agent and the development of diabetes was examined (Table 3.23). Patients prescribed clozapine ($N=75$) were excluded from this analysis due to the small treatment numbers. No patients received ziprasidone as their index antipsychotic agent. The incidence of diabetes among patients prescribed a first-generation antipsychotic was 1.6 percent compared to 2.8 percent for those prescribed risperidone. Chi-square analysis was significant ($p=0.001$) for this comparison of incidence of diabetes according to the index antipsychotic agent.

Table 3.23: Incidence of Diabetes in the Texas Medicaid Study Population and Stratified According to Age, Gender, Race/Ethnicity, Primary Mental Health Diagnosis and Index Antipsychotic Agent

Stratification	N	Percent (%)	Chi-Square p value
All ¹	382	2.4	
Age (years)			<0.001
18-34	21	0.8	
35-44	47	1.7	
45-54	73	3.3	
55-64	40	3.4	
≥ 65	201	2.8	
Gender			<0.001
Male	100	1.7	
Female	282	2.7	
Race/Ethnicity ²			<0.001
White	184	2.0	
Black	95	2.8	
Hispanic	82	3.4	
Other	21	1.7	
Primary Mental Health Diagnosis ³			0.051
Schizophrenia	49	2.0	
Bipolar Disorder	62	2.8	
Dementia	58	3.0	
Psychotic Disorder	31	2.8	
Non-Psychotic Disorder	65	3.2	
No Mental Health Diagnosis	97	2.2	

Table 3.23 (cont): Incidence of Diabetes in the Texas Medicaid Study Population and Stratified According to Age, Gender, Race/Ethnicity, Primary Mental Health Diagnosis and Index Antipsychotic Agent

Stratification	N	Percent (%)	Chi-Square p value
All ¹	382	2.4	
Antipsychotic Agent ⁴			<0.001
First-Generation Agent ⁵	80	1.6	
Olanzapine	89	2.5	
Quetiapine	25	2.4	
Risperidone	187	2.8	

¹. N=16,137 (N=3,293 Prevalent Cases excluded).

². 'Other' category comprised of Asian American, Native American and 'Other' racial/ethnic groups.

³. N= 14,124 (N=2,013 patients with a diagnosis of mental retardation excluded). Adjusted population incidence of diabetes: 2.6%.

⁴. N= 16,052 (N=75 patients treated with Clozapine excluded). Adjusted population incidence of diabetes: 2.4%.

⁵. First-generation agents included: Chlorpromazine; Fluphenazine; Haloperidol; Loxapine; Mesoridazine; Molindone; Perphenazine; Pimozide; Thioridazine; Thiothixene and Trifluoperazine.

3.3.2 Time to Occurrence of Diabetes

The mean time to occurrence of diabetes was 95.9 days (SD: 85.1) (Table 3.24), with onset ranging from seven to 362 days. As the distributions were not normally distributed (positive skew), both the mean and median time to occurrence of diabetes are reported in Table 3.24.

Table 3.24: Average Time to Occurrence (Days) of New-Onset Diabetes in the Texas Medicaid Study Population

Index Antipsychotic	N	Mean (SD)	Median
First-Generation Agent	80	82.0 (79.5)	56.0
Second-Generation Agent¹	302	99.6 (83.2)	66.0
Olanzapine	89	100.9 (82.2)	73.0
Quetiapine	25	87.0 (80.1)	51.0
Risperidone	187	100.3 (89.2)	61.0
Total	382	95.9 (85.1)	62.5

¹. N=302 new-onset cases (N=1 case treated with Clozapine excluded from further report due to small sample size).

3.3.2.1 Time to Occurrence of Diabetes According to the Class of Antipsychotic Used (Objective 4)

H_{5a}: The time to occurrence of diabetes will not differ significantly when patients are stratified according to the class of antipsychotic used (first or second-generation), after controlling for demographic, clinical and medication risk factors for diabetes.

As noted, the mean time to occurrence of diabetes was 82.0 days (SD: 79.5) for patients treated with a first-generation antipsychotic agent, and 99.6 days (SD: 83.2) for patients treated with a second-generation agent (Table 3.24). This difference was not significant when analyzed by Student T-test and the Mann-Whitney test (p=0.099 and p=0.071, respectively). Consistent with this, Cox proportional hazards regression analysis showed that, after controlling for differences in demographic, clinical and medication variables in Texas Medicaid, the class of antipsychotic agent was not significantly associated (HR: 0.902, 95% CI: 0.675 to 1.205) with the time to occurrence of diabetes (Table 3.25).

Covariates that were significantly associated with the outcome were patient age ($p=0.011$) and race/ethnicity ($p<0.001$). Compared to patients aged 18 to 34 years, the time to occurrence of diabetes was increased for patients aged 45 to 54 years (HR: 2.748, 95% CI: 1.489 to 5.072); 55 to 64 years (HR: 2.365, 95% CI: 1.165 to 4.404); and for those aged 65 years or older (HR: 1.924, 95% CI: 1.052 to 3.521). The time to onset of diabetes was increased for minority patients compared to Whites, with significant differences noted for Blacks (HR: 1.588, 95% CI: 1.192-2.117) and Hispanics (HR: 1.830, 95% CI: 1.353 to 2.475). Other covariates associated with a significant increase in time to occurrence of diabetes were female gender, and a comorbid diagnosis of hypertension or dyslipidemia (Table 3.25). In contrast, use of a concomitant diabetogenic medication and adherence to antipsychotic therapy were associated with a shorter time to occurrence of diabetes (HR=0.720, 95% CI=0.562 to 0.923; and HR=0.718, 95% CI=0.559 to 0.924, respectively).

H_{5a}: **Accepted.**

Table 3.25: Cox Regression Analysis Comparing the Time to Occurrence of Diabetes in Texas Medicaid Patients Treated with a First- or Second-Generation Antipsychotic after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Use of a Concomitant Diabetogenic Medication, Antipsychotic Adherence) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Index Antipsychotic Agent⁵					
Second-Generation Agent	-0.104 (0.148)	0.490	0.484	0.902	0.675-1.205
Adherence⁵					
MPR_365 days \geq 0.8 ⁶	-0.331 (0.128)	6.652	0.010*	0.718	0.559-0.924
Concomitant Diabetogenic Medication	-0.328 (0.127)	6.705	0.010*	0.720	0.562-0.923
Age⁵		13.107	0.011*		
35 to 44	0.523 (0.328)	2.533	0.112	1.686	0.886-3.210
45 to 54	1.011 (0.313)	10.457	0.001*	2.748	1.489-5.072
55 to 64	0.818 (0.339)	5.809	0.016*	2.365	1.165-4.404
\geq 65	0.655 (0.308)	4.509	0.034*	1.924	1.052-3.521
Gender⁵					
Female	0.269 (0.135)	3.955	<0.001*	1.309	1.004-1.706
Race/Ethnicity⁵		20.733	<0.001*		
Black	0.463 (0.147)	9.956	0.002*	1.588	1.192-2.117
Hispanic	0.604 (0.154)	15.409	<0.001*	1.830	1.353-2.475
Other ⁷	0.006 (0.260)	0.001	0.980	1.006	0.604-1.676
Primary Mental Health Diagnosis⁵		3.099	0.685		
Bipolar Disorder	0.090 (0.210)	0.183	0.669	1.094	0.725-1.652
Dementia	0.088 (0.234)	0.141	0.707	1.092	0.691-1.726
Psychotic Disorder	0.074 (0.261)	0.081	0.777	1.077	0.646-1.796
Non-Psychotic Disorder	0.318 (0.211)	2.266	0.132	1.374	0.909-2.078
No Mental Health Diagnosis	0.065 (0.204)	0.101	0.750	1.067	0.715-1.593

Table 3.25 (cont.): Cox Regression Analysis Comparing the Time to Occurrence of Diabetes in Texas Medicaid Patients Treated with a First- or Second-Generation Antipsychotic after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Use of a Concomitant Diabetogenic Medication, Antipsychotic Adherence) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Hypertension	0.949 (0.125)	57.843	0.002*	1.610	1.184-2.189
Dyslipidemia	0.476 (0.157)	9.218	<0.001*	2.583	2.023-3.298

^{1.} Model $\chi^2=173.699$, df=18, p<0.001.

^{2.} N=10,652 (Patients with prevalent diabetes, mental retardation or filling only one antipsychotic prescription excluded).

^{3.} Abbreviations: SE: Standard Error; HR = Hazard Ratio; CI = Confidence Interval.

^{4.} *Indicates statistical significance at p< 0.05.

^{5.} Reference category for each variable: Index Antipsychotic (First-Generation Agent); Adherence (MPR_365 days <0.8); Age (18-34 years); Gender (Male); Race/Ethnicity (White); Primary Mental Health Diagnosis (Schizophrenia).

^{6.} “MPR_365 days” reflects medication possession ratio calculated over a 365 day period.

^{7.} ‘Other’ category comprised of Native American, Asian American and ‘Others.’

3.3.2.2 Time to Occurrence of Diabetes According to the Specific Second-Generation Antipsychotic Agent Used (Objective 4)

H_{5b}: The time to occurrence of diabetes will not differ significantly when stratified according to the specific second-generation antipsychotic agent used, after controlling for demographic, clinical and medication risk factors for diabetes.

The time to occurrence of diabetes was analyzed according to the specific index second-generation antipsychotic agent prescribed. Patients treated with clozapine were excluded from this analysis due to the small treatment numbers. No patients received ziprasidone as their index antipsychotic agent. As shown in Table 3.24, without controlling for other variables, the time to occurrence of diabetes was shortest for quetiapine and longest for olanzapine. This finding was not significant when examined using ANOVA or Kruskal-Wallis tests (p=0.754

and $p=0.590$, respectively). When analyzed using Cox proportional hazards regression model, again no difference was noted in the time to occurrence of diabetes based on the specific second-generation antipsychotic agent used ($p=0.278$), even after controlling for differences in demographic, clinical and medication variables (Table 3.26). Hazard ratios indicated that olanzapine and quetiapine were associated with a shorter time to occurrence of diabetes compared to risperidone; however, as noted these differences were not significant (HR: 0.842, 95% CI=0.634 to 1.120; and HR: 0.726, 95% CI=0.447 to 1.178, respectively). Covariates that were significantly associated with the time to occurrence of diabetes included patient race/ethnicity, and a comorbid diagnosis with hypertension or dyslipidemia (Table 3.26). The time to onset of diabetes was increased for minority patients compared to Whites, with significant differences noted for Blacks (HR: 1.516, 95% CI: 1.109 to 2.107) and Hispanics (HR: 1.712, 95% CI: 1.223 to 2.397). While overall age was not associated with the time to occurrence of diabetes, a significant increase in the time to onset was noted for patients aged between 55 and 64 years compared to those aged 18 to 34 years (HR: 2.383, 95% CI: 1.123 to 5.059). Use of a concomitant diabetogenic medication and adherence to antipsychotic therapy were associated with a shorter time to occurrence of diabetes (HR=0.712, 95% CI=0.540 to 0.939; and HR=0.678, 95% CI=0.512 to 0.898, respectively).

H_{5b}: **Accepted.**

Table 3.26: Cox Regression Analysis Comparing the Time to Occurrence of Diabetes for Texas Medicaid Patients Treated with Second-Generation Antipsychotics after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Dose, Adherence, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Index Antipsychotic Agent⁵		2.560	0.278		
Olanzapine	-0.172 (0.145)	0.145	0.238	0.842	0.634-1.120
Quetiapine	-0.320 (0.247)	0.247	0.195	0.726	0.447-1.178
Antipsychotic Dose^{5,6}		3.554	0.169		
Moderate Dose	-0.360 (0.207)	0.207	0.082	0.698	0.465-1.047
High Dose	0.091 (0.299)	0.299	0.761	1.095	0.609-1.970
Adherence⁵					
MPR_365 days ≥ 0.8 ⁷	-0.388 (0.143)	7.360	0.007*	0.678	0.512-0.898
Concomitant Diabetogenic Medication	-0.339 (0.141)	5.769	0.016*	0.712	0.540-0.939
Age⁵		6.800	0.147		
35 to 44	0.649 (0.370)	3.087	0.079	1.914	0.928-3.950
45 to 54	0.718 (0.369)	3.782	0.052	2.050	0.994-4.225
55 to 64	0.869 (0.384)	5.115	0.024*	2.383	1.123-5.059
≥ 65	0.484 (0.356)	1.850	0.174	1.623	0.808-3.262
Gender⁵					
Female	0.144 (0.150)	0.916	0.339	1.155	0.860-1.550
Race/Ethnicity⁵		14.197	0.003*		
Black	0.416 (0.168)	6.114	0.013*	1.516	1.109-2.107
Hispanic	0.538 (0.172)	9.793	0.002*	1.712	1.223-2.397
Other ⁸	-0.172 (0.319)	0.291	0.590	0.842	0.450-1.574
Hypertension	0.928 (0.138)	45.276	<0.001*	2.530	1.931-3.315
Dyslipidemia	0.497 (0.174)	8.121	0.004*	1.644	1.168-2.314

Table 3.26 (cont.): Cox Regression Analysis Comparing the Time to Occurrence of Diabetes for Texas Medicaid Patients Treated with Second-Generation Antipsychotics after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Dose, Adherence, Use of a Concomitant Diabetogenic Medication) Variables^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Primary Mental Health Diagnosis⁵		1.203	0.945		
Bipolar Disorder	0.041 (0.251)	0.026	0.871	1.042	0.636-1.705
Dementia	0.131 (0.270)	0.234	0.628	1.140	0.671-1.937
Psychotic Disorder	0.100 (0.303)	0.108	0.742	1.105	0.611-1.999
Non-Psychotic Disorder	0.235 (0.256)	0.843	0.359	1.265	0.766-2.091
No Mental Health Diagnosis	0.070 (0.251)	0.079	0.779	1.073	0.656-1.756

^{1.} Model $\chi^2 = 132.115$, df=21, p<0.001.

^{2.} N=7,732 (Patients with prevalent diabetes, mental retardation, treated with clozapine or a first-generation antipsychotic, or filling only one prescription excluded).

^{3.} Abbreviations: SE = Standard Error; HR = Hazard Ratio; CI = Confidence Interval.

^{4.} *Indicates statistical significance at p< 0.05.

^{5.} Reference category for each variable: Index Antipsychotic (Risperidone); Dose (Low-Dose); Adherence (MPR_365 days <0.8); Age (18-34 years); Gender (Male); Race/Ethnicity (White); Primary Mental Health Diagnosis (Schizophrenia).

^{6.} Mean Daily Dose Reference Ranges: Olanzapine - Low: ≤ 10mg; Medium: >10mg to ≤ 15mg; High: >15mg; Quetiapine - Low: ≤ 300mg; Medium: >300mg to ≤ 600mg; High: >600mg; Risperidone - Low: ≤ 2mg; Medium: >2mg to ≤ 6mg; High: >6mg.

^{7.} 'MPR_356 days' reflects medication possession ratio calculated over a 365-day period.

^{8.} 'Other' category comprised of Native American, Asian American and 'Others.'

3.3.3 Incidence of Diabetes – Contributing Factors

The potential of several variables to influence the incidence of diabetes in the study population were investigated in detail. These included: the class of antipsychotic agent used (first-generation vs. second-generation); the specific type of second-generation antipsychotic agent (clozapine, olanzapine, quetiapine, risperidone or ziprasidone); the dose of the individual second-generation agents; and the primary mental health diagnosis for which these agents were presumed to be prescribed. The results of these investigations are discussed below.

3.3.3.1 Incidence of Diabetes According to the Class of Antipsychotic Agent (Objective 4)

H_{6a}: The incidence of diabetes will not differ significantly according to the class of antipsychotic agent used (first- or second-generation), after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 2.4 percent (1.6% and 2.7%, respectively of those treated with a first- or second-generation antipsychotic). After excluding patients treated with clozapine and those with a diagnosis of mental retardation from the analysis, the incidence of diabetes was 2.6 percent in the population (1.8% and 2.9%, respectively, of those treated with a first- or second-generation antipsychotic). Multivariate logistic regression analysis showed that after controlling for differences in other variables, the class of antipsychotic agent used was not significantly associated with the incidence of diabetes (Table 3.27). Compared to patients receiving a first-generation antipsychotic, the odds of new-onset diabetes increased by 21.6 percent with use of a second-generation agent; but as noted, this result was not significant (OR=1.216, 95% CI=0.905 to 1.634).

Compliance with antipsychotic therapy was significantly associated with the odds of new-onset diabetes. Compared to non-adherent patients (MPR_365 days <0.8), adherent patients were almost 3.9 times more likely to develop diabetes (OR: 3.889, 95% CI: 2.999 to 5.044). In contrast, increasing persistence with therapy was associated with a decreased odds of new-onset diabetes (OR: 0.995, 95% CI: 0.993 to 0.996). A diagnosis of comorbid hypertension or dyslipidemia were both associated with an increased odds of new-onset diabetes (OR: 2.487, 95% CI: 1.939 to 3.190; and OR: 2.020, 95% CI: 1.461 to 2.793, respectively). Women had a higher odds of new-onset diabetes compared to men (OR: 1.396, 95% CI: 1.061 to 1.837). Other variables that were significantly associated with the occurrence of new-onset diabetes were increasing patient age (p=0.007) and patient race/ethnicity (p=0.002). Compared to patients aged between 18 and 34 years, the odds of new-onset diabetes increased between 1.7 and almost three-fold for patients in the higher age strata, with the largest comparative increase for patients aged between 45 and 54 years (OR: 2.944, 95% CI: 1.581 to 5.480). With regard to race/ethnicity, the odds of new-onset diabetes were increased for Black (OR=1.454, 95% CI=1.076 to 1.965) and Hispanic patients (OR=1.722, 95% CI=1.257 to 2.360) compared to Whites.

H_{6a}: **Accepted.**

Table 3.27: Logistic Regression Analysis Comparing the Risk of New-Onset Diabetes in Texas Medicaid Patients Treated with a First-Generation versus a Second-Generation Antipsychotic after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Antipsychotic Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Intercept	-5.251 (0.343)	234.654	<0.001*	0.005	
Antipsychotic Class⁵					
Second-Generation Agent	0.196 (0.151)	1.691	0.193	1.216	0.905-1.634
Adherence⁵					
MPR_365 days \geq 0.8 ^{3,6}	1.358 (0.133)	104.793	<0.001*	3.889	2.999-5.044
Persistence	-0.004 (0.001)	75.567	<0.001*	0.995	0.993-0.996
Age⁵		14.174	0.007*		
35 to 44	0.557 (0.332)	2.814	0.093	1.746	0.910-3.348
45 to 54	1.080 (0.317)	11.591	<0.001*	2.944	1.581-5.480
55 to 64	1.922 (0.344)	7.178	0.007*	2.513	1.281-4.932
\geq 65	0.757 (0.312)	5.868	0.015*	2.132	1.155-3.933
Gender⁵					
Female	0.334 (0.154)	5.947	0.017*	1.396	1.061-1.837
Race/Ethnicity⁵		14.927	0.002*		
Black	0.375 (0.154)	5.947	0.015*	1.454	1.076-1.965
Hispanic	0.544 (0.161)	11.435	<0.001*	1.722	1.257-2.360
Other ⁷	-0.069 (0.270)	0.066	0.798	0.933	0.550-1.583
Hypertension	0.911 (0.127)	51.496	<0.001*	2.487	1.939-3.190
Dyslipidemia	0.703 (0.165)	18.118	<0.001*	2.020	1.461-2.793
Concomitant Diabetogenic Medication	-0.080 (0.132)	0.364	0.546	0.923	0.712-1.196

Table 3.27 (cont): Logistic Regression Analysis Comparing the Risk of New-Onset Diabetes in Texas Medicaid Patients Treated with a First-Generation versus a Second-Generation Antipsychotic after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Antipsychotic Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Primary Mental Health Diagnosis⁵		5.108	0.403		
Bipolar Disorder	0.058 (0.217)	0.071	0.790	1.060	0.692-1.622
Dementia	0.152 (0.241)	0.400	0.527	1.165	0.726-1.867
Psychotic Disorder	0.027 (0.269)	0.010	0.921	1.027	0.606-1.741
Non-Psychotic Disorder	0.401 (0.217)	3.416	0.065	1.493	0.976-2.284
No Mental Health Diagnosis	0.079 (0.211)	0.139	0.709	1.082	0.716-1.634

^{1.} Model $\chi^2 = 266.411$, df = 19, p < 0.001.

^{2.} N=10,953 (Patients with mental retardation, prevalent diabetes and those filling only one antipsychotic prescription excluded: N=8,477).

^{3.} Abbreviations: SE = Standard Error; OR = Odds Ratio; CI = Confidence Interval; MPR = Medication Possession Ratio.

^{4.} * Indicates statistical significance at p < 0.05.

^{5.} Reference category for each variable: Antipsychotic Class (First-Generation Agent); Adherence (MPR_365 days < 0.8); Age 18-34 years; Race/Ethnicity (White); Gender (Male); Primary Mental Health Diagnosis (Schizophrenia).

^{6.} 'MPR_365 days' refers to adherence measured over a 365-day period.

^{7.} 'Other' category comprised of Native American, Asian American and 'Others.'

3.3.3.2 Incidence of Diabetes According to the Specific Second-Generation Antipsychotic Agent (Objective 4)

H_{6b}: The incidence of diabetes will not differ significantly according to the specific second-generation antipsychotic agent used, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 2.9 percent (olanzapine: 2.7%; quetiapine: 2.6%; risperidone: 3.1%) among eligible patients taking a second-generation antipsychotic after excluding those treated with clozapine and those with a diagnosis of mental retardation from the analysis. Multivariate logistic regression analysis showed that after controlling for differences in other variables, there was no difference ($p=0.281$) in the incidence of diabetes according to the specific second-generation antipsychotic prescribed (Table 3.28). Compared to patients receiving risperidone, the odds of new-onset diabetes were reduced by 12.1 percent with olanzapine (OR=0.879, 95% CI=0.653 to 1.184), and by 31.7 percent with quetiapine (OR=0.683, 95% CI=0.414 to 1.126); but as noted, these results were not significant.

While the choice of antipsychotic did not alter the odds of new-onset diabetes, compliance with therapy was significantly associated with the outcome. Compared to non-adherent patients (MPR_365 days <0.8), adherent patients were 3.7 times more likely to develop diabetes (OR: 3.710, 95% CI: 2.777 to 4.956). In contrast, increasing persistence with therapy was associated with a marginally decreased odds of new-onset diabetes (OR: 0.995, 95% CI: 0.993 to 0.996).

Diagnoses of comorbid hypertension or dyslipidemia were associated with an increased odds of new-onset diabetes (OR: 2.480, 95% CI: 1.881 to 3.269; and OR: 2.034, 95% CI: 1.418 to 2.916, respectively) however, the type of

mental health diagnosis for which the antipsychotic was presumed to be prescribed was not associated with the outcome ($p=0.683$). Patient race/ethnicity was again significantly associated with the occurrence of new-onset diabetes ($p=0.020$). Compared to Whites, the odds of new-onset diabetes increased for Hispanic patients (OR=1.612, 95% CI=1.133 to 2.294). While overall age was not associated with the risk of new-onset diabetes, an increase in risk was noted for patients aged between 45 and 54 years (OR: 2.222, 95% CI: 1.066 to 4.634), 55 and 64 years (OR: 2.748, 95% CI: 1.280 to 5.900), and those aged 65 years or older (OR: 1.232, 95% CI: 1.006 to 4.130) when compared to patients aged between 18 and 34 years.

H_{6b}: **Accepted.**

Table 3.28: Logistic Regression Analysis Comparing the Risk of New-Onset Diabetes in Texas Medicaid Patients Treated with Specific Second-Generation Antipsychotic Agents after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Antipsychotic Dose, Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Intercept	-4.371 (0.404)	136.931	<0.001*	0.009	
Antipsychotic Agent⁵		2.537	0.281		
Olanzapine	-0.128 (0.152)	0.717	0.397	0.879	0.653-1.184
Quetiapine	0.381 (0.255)	2.233	0.135	0.683	0.414-1.126
Antipsychotic Dose^{5,6}		2.590	0.274		
Medium Dose	-0.294 (0.208)	1.987	0.159	0.746	0.496-1.121
High Dose	0.148 (0.304)	0.236	0.627	1.159	0.639-2.104
Adherence⁵					
MPR_365 days \geq 0.8 ⁷	1.311 (0.148)	76.648	<0.001*	3.710	2.777-4.956
Persistence	-0.005 (0.001)	64.997	<0.001*	0.995	0.993-0.996
Age⁵		7.000	0.136		
35 to 44	0.727 (0.375)	3.758	0.053	2.069	0.992-4.314
45 to 54	0.799 (0.375)	4.536	0.033*	2.222	1.066-4.634
55 to 64	1.011 (0.390)	6.727	0.009*	2.748	1.280-5.900
\geq 65	0.712 (0.360)	3.907	0.048*	1.232	1.006-4.130
Gender⁵					
Female	0.209 (0.156)	1.797	0.180	1.232	0.908-1.673
Race/Ethnicity⁵		9.859	0.020*		
Black	0.310 (0.176)	3.084	0.079	1.363	0.965-1.925
Hispanic	0.478 (0.180)	7.044	0.008*	1.612	1.133-2.294
Other ⁸	-0.236 (0.330)	0.509	0.475	0.790	0.413-1.510

Table 3.28 (cont.): Logistic Regression Analysis Comparing the Risk of New-Onset Diabetes in Texas Medicaid Patients Treated with Specific Second-Generation Antipsychotic Agents after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Mental Health Diagnosis, Hypertension, Dyslipidemia) and Medication (Antipsychotic Dose, Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Primary Mental Health Diagnosis⁵		3.113	0.683		
Bipolar Disorder	0.008 (0.260)	0.001	0.976	1.008	0.606-1.676
Dementia	0.196 (0.278)	0.495	0.482	1.216	0.705-2.099
Psychotic Disorder	0.029 (0.312)	0.009	0.926	1.030	0.559-1.898
Non-Psychotic Disorder	0.337 (0.263)	1.645	0.200	1.401	0.837-2.345
No Mental Health Diagnosis	0.074 (0.256)	0.083	0.773	1.077	0.651-1.780
Hypertension	0.908 (0.141)	41.517	<0.001*	2.480	1.881-3.269
Dyslipidemia	0.710 (0.184)	14.911	<0.001*	2.034	1.418-2.916
Concomitant Diabetogenic Medication	-0.091 (0.147)	0.377	0.539	0.913	0.684-1.219

^{1.} Model $\chi^2 = 200.212$, df = 22, p<0.001.

^{2.} N=7,842 (Patients with mental retardation, prevalent diabetes, patients treated with clozapine, filling only one antipsychotic prescription and dose outliers excluded: N=5,889).

^{3.} Abbreviations: SE – Standard Error; OR = Odds Ratio; CI = Confidence Interval; MPR = Medication Possession Ratio.

^{4.} *Indicates statistical significance at p< 0.05.

^{5.} Reference category for each variable: Index Antipsychotic (Risperidone); Race/Ethnicity (White); Gender (Male); Age (18-34 years); Primary Mental Health Diagnosis (Schizophrenia); Adherence (MPR_365 days <0.8) Dose (Low-Dose).

^{6.} Mean Daily Dose Reference Ranges: Olanzapine - Low: ≤ 10mg; Medium: >10mg to ≤ 15mg; High: >15mg; Quetiapine - Low: ≤ 300mg; Medium: >300mg to ≤ 600mg; High: >600mg; Risperidone - Low: ≤ 2mg; Medium: >2mg to ≤ 6mg; High: >6mg.

^{7.} 'MPR_365 days' reflects medication possession ratio calculated over a 365-day period.

^{8.} 'Other' category comprised of Native American, Asian American and 'Others.'

3.3.3.3 Incidence of Diabetes According to Antipsychotic Dose (Objective 4)

A central theory in this study was the possibility that the incidence of diabetes may be associated with the dose of antipsychotic used. The association between treatment dose for olanzapine, quetiapine and risperidone and the incidence of diabetes are reported in the following section. Hypotheses 7a and 7e relating to clozapine and ziprasidone, respectively, were not tested due to the inadequate sample sizes.

3.3.3.3.1 Incidence of Diabetes According to the Mean Daily Dose of Olanzapine

H_{7b}: The incidence of diabetes will not differ significantly according to the dose of olanzapine used, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 2.9 percent (N=74) for patients treated with olanzapine, after excluding those with prevalent diabetes, a diagnosis of mental retardation, and patients who redeemed only one prescription from the analysis. Multivariate logistic regression analysis showed that, after controlling for differences in other variables, the incidence of diabetes did not differ according to the dose of olanzapine used (OR: 1.019, 95% CI: 0.976 to 1.065) (Table 3.29).

While the dose of olanzapine did not alter the odds of new-onset diabetes, compliance with therapy was significantly associated with the outcome. Compared to non-adherent patients (MPR₃₆₅ days <0.8), adherent patients were approximately 2.5 times more likely to develop diabetes (OR: 2.485, 95% CI: 1.449 to 4.262). In contrast, increasing persistence with therapy was associated with a decreased odds of new-onset diabetes (OR: 0.995, 95% CI: 0.993 to 0.998). Diagnosis of comorbid hypertension was associated with an

increased odds of new-onset diabetes (OR: 2.543, 95% CI: 1.525 to 4.240). The relevance of mental health diagnoses will be discussed in hypothesis 8b.

H_{7b}: **Accepted.**

Table 3.29: Logistic Regression Analysis of the Association between Mean Daily Dose and Primary Mental Health Diagnosis for Texas Medicaid Patients Treated with Olanzapine and Risk of New-Onset Diabetes after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Hypertension, Dyslipidemia) and Medication (Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Intercept	-5.002 (0.657)	657.865	<0.001*	0.007	
Mean Daily Dose	0.019 (0.022)	0.759	0.384	1.019	0.976-1.065
Adherence ^{5,6}					
MPR_365 days \geq 0.8 ³	0.910 (0.275)	10.929	<0.001*	2.485	1.449-4.262
Persistence	-0.005 (0.001)	15.150	<0.001*	0.995	0.993-0.998
Age ⁵		1.582	0.812		
35 to 44	0.467 (0.544)	0.737	0.391	1.595	0.549-4.634
45 to 54	0.595 (0.550)	1.167	0.280	1.812	0.616-5.331
55 to 64	0.712 (0.600)	1.408	0.235	2.037	0.629-6.600
\geq 65	0.497 (0.543)	0.836	0.360	1.643	0.567-4.765
Gender ⁵					
Female	0.547 (0.297)	3.407	0.065	1.729	0.967-3.091
Race/Ethnicity ⁵		1.353	0.717		
Black	0.378 (0.335)	1.272	0.259	1.459	0.757-2.813
Hispanic	0.128 (0.323)	0.158	0.691	1.137	0.604-2.140
Other ⁷	-0.019 (0.500)	0.001	0.969	1.981	0.368-2.614
Hypertension	0.933 (0.261)	12.798	<0.001*	2.543	1.525-4.240
Dyslipidemia	0.031 (0.386)	0.001	0.973	1.013	1.476-2.158
Concomitant Diabetogenic Medication	-0.291 (0.279)	1.087	0.297	0.748	0.433-1.292

Table 3.29 (cont.): Logistic Regression Analysis of the Association between Mean Daily Dose and Primary Mental Health Diagnosis for Texas Medicaid Patients Treated with Olanzapine and Risk of New-Onset Diabetes after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Hypertension, Dyslipidemia) and Medication (Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Primary Mental Health Diagnosis⁵		12.047	0.034*		
Bipolar Disorder	0.116 (0.444)	0.069	0.793	1.123	0.470-2.682
Dementia	-0.198 (0.556)	0.127	0.722	0.820	0.276-2.441
Psychotic Disorder	1.069 (0.502)	4.529	0.033*	2.911	1.088-7.790
Non-Psychotic Disorder	0.889 (0.433)	4.227	0.040*	2.433	1.042-5.680
No Mental Health Diagnosis	0.521 (0.419)	1.542	0.214	1.683	0.740-3.827

^{1.} Model $\chi^2 = 54.652$, df = 19, p<0.001.

^{2.} N=2,521 (Patients with mental retardation, prevalent diabetes, dose outliers and those filling only one antipsychotic prescription excluded: N=1,678).

^{3.} Abbreviations: OR = Odds Ratio; CI = Confidence Interval; MPR_365 days = Medication Possession Ratio over 365 days.

^{4.} *Indicates statistical significance at p< 0.05.

^{5.} Reference category for each variable: Age (18-34 years); Race/Ethnicity (White); Gender (Male); Primary Mental Health Diagnosis (Schizophrenia); Adherence (MPR_365 days <0.8).

^{6.} 'MPR_356 days' reflects medication possession ratio calculated over a 365-day period.

^{7.} 'Other' category comprised of Native American, Asian American and 'Others.'

3.3.3.3.2 Incidence of Diabetes According to the Mean Daily Dose of Quetiapine

H_{7c}: The incidence of diabetes will not differ significantly according to the dose of quetiapine used, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 2.7 percent (N=19) for patients treated with quetiapine after excluding those with prevalent diabetes, a diagnosis of mental retardation, and patients filling only one prescription from the analysis. Multivariate logistic regression analysis showed that, after controlling for differences in other variables, there was no association between quetiapine dose and incidence of diabetes (OR: 1.001, 95% CI: 0.997 to 1.004) (Table 3.30). The only variables that were significantly associated with the occurrence of diabetes in patients taking quetiapine therapy were adherence and persistence to quetiapine therapy. Compared to non-adherent patients (MPR_365 days <0.8), adherent patients were 10.7 times more likely to develop diabetes (OR: 10.657, 95% CI: 3.141 to 36.161). Increasing persistence with therapy was however associated with a decreased odds of new-onset diabetes (OR: 0.993, 95% CI: 0.988 to 0.997). The relevance of mental health diagnoses will be discussed in hypothesis 8c.

H_{7c}: **Accepted.**

Table 3.30: Logistic Regression Analysis of the Association between Mean Daily Dose and Primary Mental Health Diagnosis for Texas Medicaid Patients Treated with Quetiapine and Risk of New-Onset Diabetes after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Hypertension, Dyslipidemia) and Medication (Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Intercept	-4.126 (1.148)	12.922	<0.001*	0.016	
Mean Daily Dose	0.000 (0.002)	0.082	0.774	1.001	0.997-1.004
Adherence ^{5,6}					
MPR_365 days \geq 0.8 ²	2.366 (0.623)	14.408	<0.001*	10.657	3.141-36.161
Persistence	-0.007 (0.002)	9.848	0.002*	0.993	0.988-0.997
Age ⁵		0.771	0.680		
45 to 64	-0.401 (0.846)	0.225	0.636	0.670	0.128-3.517
\geq 65	0.283 (0.751)	0.142	0.707	1.327	0.304-5.787
Gender ⁵					
Female	-0.038 (0.565)	0.004	0.947	0.963	0.318-2.914
Race/Ethnicity ⁵		1.515	0.679		
Black	-0.352 (0.818)	0.185	0.667	0.703	0.142-3.497
Hispanic	-0.370 (1.090)	0.115	0.734	0.691	0.082-5.847
Other ⁶	0.870 (0.865)	1.012	0.314	2.387	0.438-12.999
Hypertension	0.082 (0.536)	0.023	0.879	1.085	0.379-3.102
Dyslipidemia	0.690 (0.667)	1.070	0.301	1.993	0.540-7.360
Concomitant Diabetogenic Medication	-0.227 (0.561)	0.164	0.686	0.797	0.266-2.391

Table 3.30 (cont): Logistic Regression Analysis of the Association between Mean Daily Dose and Primary Mental Health Diagnosis for Texas Medicaid Patients Treated with Quetiapine and Risk of New-Onset Diabetes after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Hypertension, Dyslipidemia) and Medication (Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Primary Mental Health Diagnosis⁵		1.988	0.851		
Bipolar Disorder	0.350 (0.914)	0.147	0.701	1.420	0.237-8.512
Dementia	-0.195 (1.075)	0.033	0.856	0.823	0.100-6.754
Psychotic Disorder	-1.063 (1.365)	0.607	0.436	0.345	0.024-5.014
Non-Psychotic Disorder	-0.169 (1.051)	0.026	0.872	0.844	0.108-6.623
No Mental Health Diagnosis	-0.439 (1.067)	0.169	0.681	0.645	0.080-5.220

^{1.} Model $\chi^2 = 27.927$ df = 17, p=0.046.

^{2.} N=700 (Patients with mental retardation, prevalent diabetes, dose outliers and those filling only one antipsychotic prescription excluded: N=531).

^{3.} Abbreviations: OR = Odds Ratio; CI = Confidence Interval; MPR_365 days = Medication Possession Ratio over 365 days.

^{4.} *Indicates statistical significance at p< 0.05.

^{5.} Reference category for each variable: Age (< 45 years); Race/Ethnicity (White); Gender (Male); Primary Mental Health Diagnosis (Schizophrenia); Adherence (MPR_365 days <0.8).

^{6.} 'MPR_356 days' reflects medication possession ratio calculated over a 365-day period.

^{7.} 'Other' category comprised of Native American, Asian American and 'Others.'

3.3.3.3 Incidence of Diabetes According to the Mean Daily Dose of Risperidone

H_{7d}: The incidence of diabetes will not differ significantly according to the dose of risperidone used, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 3.3 percent (N=153) for patients treated with risperidone after excluding those with prevalent diabetes, a diagnosis of mental retardation, and patients filling only one prescription from the analysis. Multivariate logistic regression analysis showed that, after controlling for differences in other variables, there was no association between the incidence of diabetes and the dose of risperidone used (OR: 0.970, 95% CI: 0.854 to 1.102) (Table 3.31). Variables that were significantly associated with the incidence of diabetes were a diagnosis of hypertension (OR: 2.790, 95% CI: 1.957 to 3.976), or dyslipidemia (OR: 2.988, 95% CI: 1.916 to 4.659), and adherence to antipsychotic therapy (OR: 4.284, 95% CI: 2.928 to 6.163). Increasing persistence with therapy was associated with decreased odds of new-onset diabetes (OR: 0.994; 95% CI: 0.993 to 0.996). Patient race/ethnicity was also associated with the incidence of diabetes in patients prescribed risperidone (p=0.004). Compared to White patients, Black and Hispanic patients had increased odds of developing new-onset diabetes (OR: 1.586; 95% CI: 1.027 to 2.451; and OR: 1.874; 95% CI: 1.210 to 2.901, respectively). While overall age was not associated with the risk of new-onset diabetes, an increase in risk was noted for patients aged between 55 and 64 years, compared to those aged between 18 and 34 years (OR: 4.267; 95% CI: 1.372 to 13.268). The relevance of mental health diagnoses will be discussed in hypothesis 8d.

H_{7d}: **Accepted.**

Table 3.31: Logistic Regression Analysis of the Association between Mean Daily Dose and Primary Mental Health Diagnosis for Texas Medicaid Patients Treated with Risperidone and Risk of New-Onset Diabetes after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Hypertension, Dyslipidemia) and Medication (Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Intercept	-5.017 (0.625)	64.339	<0.001*	0.007	
Mean Daily Dose	-0.031 (0.065)	0.221	0.639	0.970	0.854-1.102
Adherence⁵					
MPR_365 days \geq 0.8 ²	1.446 (0.190)	58.065	<0.001*	4.248	2.928-6.163
Persistence	-0.006 (0.001)	42.232	<0.001*	0.994	0.993-0.996
Age⁵		6.881	0.142		
35 to 44	0.963 (0.584)	2.723	0.099	2.620	0.835-8.223
45 to 54	0.976 (0.578)	2.850	0.091	2.653	0.855-8.238
55 to 64	1.451 (0.579)	6.281	0.012*	4.267	1.372-13.268
\geq 65	0.996 (0.555)	3.224	0.073	2.707	0.913-8.030
Gender⁵					
Female	0.071 (0.195)	0.131	0.717	1.073	0.732-1.573
Race/Ethnicity⁵		13.444	0.004*		
Black	0.461 (0.222)	4.319	0.038*	1.586	1.027-2.451
Hispanic	0.628 (0.223)	7.916	0.005*	1.874	1.210-2.901
Other ⁶	-0.760 (0.5340)	2.022	0.155	0.468	0.164-1.333
Hypertension	1.026 (0.181)	32.211	<0.001*	2.790	1.957-3.976
Dyslipidemia	1.094 (0.227)	23.304	<0.001*	2.988	1.916-4.659
Concomitant Diabetogenic Medication	0.055 (0.185)	0.087	0.768	1.056	0.735-1.518

Table 3.31 (cont.): Logistic Regression Analysis of the Association between Mean Daily Dose and Primary Mental Health Diagnosis for Texas Medicaid Patients Treated with Risperidone and Risk of New-Onset Diabetes after Controlling for Demographic (Age, Gender, Race/Ethnicity), Clinical (Hypertension, Dyslipidemia) and Medication (Compliance, Use of a Concomitant Diabetogenic Medication) Variables ^{1,2}

Variables	β (SE) ³	Wald F	p ⁴	OR ³	95% CI ³
Primary Mental Health Diagnosis⁵		6.147	0.292		
Bipolar Disorder	-0.214 (0.354)	0.365	0.545	0.807	0.403-1.616
Dementia	0.248 (0.359)	0.476	0.490	1.282	0.634-2.593
Psychotic Disorder	-0.487 (0.427)	1.300	0.254	0.614	0.266-1.420
Non-Psychotic Disorder	0.124 (0.355)	0.122	0.727	1.132	0.565-2.269
No Mental Health Diagnosis	-0.107 (0.344)	0.097	0.755	0.898	0.457-1.764

^{1.} Model $\chi^2 = 160.747$, df = 19, p<0.001.

^{2.} N=4,621 (Patients with mental retardation, prevalent diabetes, dose outliers and those filling only one antipsychotic prescription excluded: N=3,587).

^{3.} Abbreviations: OR = Odds Ratio; CI = Confidence Interval; MPR_365 days = Medication Possession Ratio over 365 days.

^{4.} *Indicates statistical significance at p< 0.05.

^{5.} Reference category for each variable: Age (18-34 years); Race/Ethnicity (White); Gender (Male); Primary Mental Health Diagnosis (Schizophrenia); Adherence (MPR_365 days <0.8).

^{6.} 'MPR_356 days' reflects medication possession ratio calculated over a 365-day period.

^{7.} 'Other' category comprised of Native American, Asian American and 'Others.'

3.3.3.4 Incidence of Diabetes According to Primary Mental Health Diagnosis (Objective 4)

Another key theory in this study was the possibility that the incidence of diabetes may be associated with the primary mental health diagnosis for which antipsychotic therapy was presumed to be prescribed. The association between the presumed indication for olanzapine, quetiapine and risperidone and the incidence of diabetes are reported in the following section. Hypotheses 8a and 8e relating to clozapine and ziprasidone, respectively, were not tested due to inadequate sample size.

3.3.3.4.1 Incidence of Diabetes with Olanzapine According to the Primary Mental Health Diagnosis

H_{8b}: For patients treated with olanzapine, the incidence of diabetes will not differ significantly when stratified according to primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 2.9 percent (N=74) for patients treated with olanzapine, after excluding those with prevalent diabetes, a diagnosis of mental retardation, and patients who redeemed only one prescription from the analysis. Multivariate logistic regression analysis showed that, after controlling for differences in other variables, the incidence of diabetes differed according to the primary mental health diagnosis for which olanzapine was presumed to be used ($p=0.034$) (Table 3.29). With the exception of patients with dementia, the odds of developing new-onset diabetes were increased for all diagnostic groups when compared to schizophrenia. Only two contrasts were significant, however. Patients with a psychotic disorder other than schizophrenia were 2.9 times more likely to develop diabetes than those with schizophrenia (OR: 2.911, 95% CI: 1.088 to 7.790). Similarly, patients with a non-psychotic disorder had a 2.4-fold increase in odds of diabetes compared to those with schizophrenia (OR: 2.433, 95% CI: 1.042 to 5.680).

H_{8b}: Rejected.

3.3.3.4.2 Incidence of Diabetes with Quetiapine According to Primary Mental Health Diagnosis

H_{8c}: For patients treated with quetiapine, the incidence of diabetes will not differ significantly when stratified according to primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 2.7 percent (N=19) for patients treated with quetiapine after excluding those with prevalent diabetes, a diagnosis of mental retardation, and patients who redeemed only one prescription from the analysis. Multivariate logistic regression analysis showed that, after controlling for differences in other variables, the incidence of diabetes did not differ according to the primary mental health diagnosis for which quetiapine was presumed to be prescribed ($p=0.851$) (Table 3.30). With the exception of bipolar disorder, the odds of developing new-onset diabetes were reduced for all diagnostic categories when compared to schizophrenia; however, none of these contrasts were significant.

H_{8c}: **Accepted.**

3.3.3.4.3 Incidence of Diabetes with Risperidone According to Primary Mental Health Diagnosis

H_{8d}: For patients treated with risperidone, the incidence of diabetes will not differ significantly according to primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.

The incidence of diabetes was 3.3 percent (N=153) for patients treated with risperidone after excluding those with prevalent diabetes, a diagnosis of mental retardation, and patients who redeemed only one prescription from the analysis. Multivariate logistic regression analysis showed that after controlling for differences in other variables, the incidence of diabetes did not differ according to the primary mental health diagnosis for which risperidone was presumed to be prescribed ($p=0.292$) (Table 3.31). Compared to patients with schizophrenia, the odds of new-onset diabetes were increased for patients with dementia or a non-psychotic disorder, and reduced for those with bipolar disorder, a psychotic disorder or no mental health diagnosis. None of these contrasts were significant, however.

H_{8d}: Accepted.

3.4 Summary

Included in this chapter were a description of the study population and an analysis of the study objectives. It was comprised of 19,430 eligible patients, the majority of whom were older, white women. Differences were found in the choice of antipsychotic agent when examined according to age, gender, race/ethnicity and mental health diagnosis, with differences in the prescribed dose of antipsychotic noted when examined according to patient age and mental health diagnosis. Compliance with antipsychotic therapy varied according to patient age, race/ethnicity, mental health diagnosis and antipsychotic agent. Logistic regression analysis examining the prevalence of diabetes in the population revealed differences in prevalence rates based on mental health diagnoses. Regarding the central theme of the association between antipsychotic use and the risk of new-onset diabetes, no difference was found between the different classes of antipsychotic (first-generation vs. second-generation), between the specific second-generation agents (olanzapine, quetiapine, or risperidone), based on antipsychotic treatment indication for the second-generation agents olanzapine, quetiapine and risperidone, or based on treatment dose for quetiapine or risperidone. Table 3.32 summarizes the results of the hypothesis testing for objectives two, three and four.

Table 3.32: Summary of Hypotheses Testing

Hypotheses	Results
Phase I: Demographic and Antipsychotic Utilization Patterns (Objective 2)	
H _{1a} : The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient age.	Rejected
H _{1b} : The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient gender.	Rejected
H _{1c} : The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient race/ethnicity.	Rejected
H _{1d} : The percentage of patients treated with the different antipsychotic agents will not differ significantly when stratified according to patient primary mental health diagnosis.	Rejected
H _{2a} : The classification of mean daily antipsychotic dose as ‘Low,’ ‘Medium,’ or ‘High’ dose will not differ significantly when stratified according to the second-generation antipsychotic agent used.	Rejected
H _{2b} : The mean daily antipsychotic dose for clozapine will not differ significantly when stratified according to patient age.	Not tested
H _{2c} : The mean daily antipsychotic dose for olanzapine will not differ significantly when stratified according to patient age.	Rejected
H _{2d} : The mean daily antipsychotic dose for quetiapine will not differ significantly when stratified according to patient age.	Rejected
H _{2e} : The mean daily antipsychotic dose for risperidone will not differ significantly when stratified according to patient age.	Rejected
H _{2f} : The mean daily antipsychotic dose for ziprasidone will not differ significantly when stratified according to patient age.	Not tested
H _{2g} : The mean daily antipsychotic dose for the clozapine will not differ significantly when stratified according to primary mental health diagnosis.	Not tested
H _{2h} : The mean daily antipsychotic dose for olanzapine will not differ significantly when stratified according to primary mental health diagnosis.	Rejected
H _{2i} : The mean daily antipsychotic dose for quetiapine will not differ significantly when stratified according to primary mental health diagnosis.	Rejected
H _{2j} : The mean daily antipsychotic dose for risperidone will not differ significantly when stratified according to primary mental health diagnosis.	Rejected
H _{2k} : The mean daily antipsychotic dose for ziprasidone will not differ significantly when stratified according to primary mental health diagnosis.	Not tested

Table 3.32: Summary of Hypotheses Testing

Hypotheses	Results
Phase I: Demographic and Antipsychotic Utilization Patterns (Objective 2)	
H _{3a} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient age.	Rejected
H _{3b} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient age.	Rejected
H _{3c} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient gender.	Rejected
H _{3d} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient gender.	Accepted
H _{3e} : Adherence with antipsychotic therapy will not differ significantly when stratified according to patient race/ethnicity.	Rejected
H _{3f} : Persistence with antipsychotic therapy will not differ significantly when stratified according to patient race/ethnicity.	Rejected
H _{3g} : Adherence with antipsychotic therapy will not differ significantly when stratified according to primary mental health diagnosis.	Rejected
H _{3h} : Persistence with antipsychotic therapy will not differ significantly when stratified according to primary mental health diagnosis.	Rejected
H _{3i} : Adherence with antipsychotic therapy will not differ significantly when stratified according to antipsychotic agent.	Rejected
H _{3j} : Persistence with antipsychotic therapy will not differ significantly when stratified according to antipsychotic agent.	Rejected
Phase II: Prevalence of Diabetes (Objective 3)	
H _{4a} : The prevalence of diabetes will not differ significantly when stratified according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Rejected
Phase III: Incidence of Diabetes (Objective 4)	
H _{5a} : The time to occurrence of diabetes will not differ significantly when patients are stratified according to the class of antipsychotic used, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{5b} : The time to occurrence of diabetes will not differ significantly when patients are stratified according to the specific second-generation antipsychotic used, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted

Table 3.32 (cont.): Summary of Hypotheses Testing

Hypotheses	Results
Phase III: Incidence of Diabetes (Objective 4)	
H _{6a} : The incidence of diabetes will not differ significantly according to the class of antipsychotic used (first-generation vs. second-generation), after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{6b} : The incidence of diabetes will not differ significantly according to the specific second-generation antipsychotic used, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{7a} : The incidence of diabetes will not differ significantly according to the dose of clozapine used, after controlling for demographic, clinical and medication risk factors for diabetes.	Not tested
H _{7b} : The incidence of diabetes will not differ significantly according to the dose of olanzapine used, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{7c} : The incidence of diabetes will not differ significantly according to the dose of quetiapine used, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{7d} : The incidence of diabetes will not differ significantly according to the dose of risperidone used, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{7e} : The incidence of diabetes will not differ significantly according to the dose of ziprasidone used, after controlling for demographic, clinical and medication risk factors for diabetes.	Not tested
H _{8a} : For patients treated with clozapine, the incidence of diabetes will not differ significantly according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Not tested
H _{8b} : For patients treated with olanzapine, the incidence of diabetes will not differ significantly according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Rejected
H _{8c} : For patients treated with quetiapine the incidence of diabetes will not differ significantly when stratified according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{8d} : For patients treated with risperidone the incidence of diabetes will not differ significantly according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Accepted
H _{8e} : For patients treated with ziprasidone the incidence of diabetes will not differ significantly according to the primary mental health diagnosis, after controlling for demographic, clinical and medication risk factors for diabetes.	Not tested

Chapter 4: Discussion

This chapter provides a detailed discussion of the study results. First, the goals of the study are summarized briefly. The results are then reviewed according to the study phases: Phase I - demographic and antipsychotic utilization patterns; Phase II – the prevalence of diabetes; and Phase III – the incidence of diabetes in the study population. Possible explanations for the study findings are proposed, and the potential implications of the study reported. Following a review of the study limitations, directions for future research in this area are suggested.

4.1 Review of Study Goals

The primary goals of this study were to determine the impact of antipsychotic dose and treatment indication on the relative risk of new-onset diabetes associated with the second-generation antipsychotic agents. Secondary goals included: profiling the demographic characteristics and antipsychotic utilization patterns of the study population, and examining the prevalence of diabetes in this cohort. These goals were addressed using Texas Medicaid data for a five-year period from 1997 to 2001. The study expanded on findings from previous investigations by investigating the impact of dose and treatment indication, while controlling for a wide-range of demographic, clinical and medication risk factors for diabetes. The large sample size in this study allowed sufficient statistical power to detect differences between the antipsychotic agents.

4.2 Study Objectives

Four study objectives were addressed in this study. The results for each of these will now be discussed in the context of the available literature in this area.

4.2.1 Objective 1: Epidemiology

The first objective of this study was to describe the demographic and clinical characteristics of the study population. Patients aged 18 years and older enrolled in Texas Medicaid who received antipsychotic monotherapy served as the study cohort. Of 129,860 patients who redeemed a prescription for an antipsychotic agent, 19,430 met the eligibility criteria for this phase.

4.2.1.1 Demographic Variables

The average patient age was 60.3 years (SD: 21.9), with patients aged 65 years or older most commonly (47.6%) represented. Women accounted for 65.7 percent of the population, and were significantly older than their male counterparts, with a mean age difference of 12 years between the groups. The majority of enrollees were White (55.1%), with minorities, and in particular Blacks (21.4%) over-represented in this study population. These demographics are consistent with those expected from an adult Medicaid population.³⁶⁷ Compared to published studies in this area, patients were on average older and more likely to be female in this dataset.^{3;4;9;10;225-241;243;245-252;378;379}

The majority of these studies did not report the race/ethnicity of the study population. Typically, higher percentages of White enrollees (range: 61-73 %) were noted in studies reporting race/ethnicity when compared to this study.^{227;228;235;239;249;251;252} In a study involving patients with schizophrenia enrolled in California Medicaid, a comparable 54.9 percent of the population was White.²²⁶ Higher percentages of non-white enrollees were reported in two studies which used claims data from hospital inpatient and ambulatory care clinics for indigent

patients.^{225;233} The demographic differences between this study and the published literature can be explained by the nature of the database (that is, a care provider for the indigent and disabled) and the fact that unlike a number of published studies, this study did not restrict eligibility to specific diagnostic categories, or to patients aged 65 years or less.

Both the prevalence and incidence of diabetes vary by age and race/ethnicity, being higher in older adults, Blacks and Hispanics.^{201;202;224;276} Based on the demographics of this study population, both the prevalence and annual incidence of diabetes would be expected to exceed rates reported in previous studies and the national age-adjusted estimates of 8.7 percent and 0.7 percent, respectively.^{201;276} As noted in Chapter 1 (section 1.11.3.3), although systematically different from the general U.S. population, the Medicaid database is generalizable to patients receiving antipsychotic therapy, that is, for patients with serious mental illness, indigent patients, and those who are elderly or infirm in receipt of long-term care.

4.2.1.2 Clinical Variables

A number of clinical variables with the potential to confound the relationship between antipsychotic exposure and development of diabetes were examined in the study. These included mental health diagnoses, hypertension and dyslipidemia. The prevalence of these conditions in this population relative to the published literature and the potential impact on the study findings will now be discussed.

4.2.1.2.1 Primary Mental Health Diagnosis

The indication for which an antipsychotic was presumed to be prescribed was a primary consideration. Patients with schizophrenia or bipolar disorder appear to be at an increased risk of diabetes, independent of antipsychotic use.¹³⁻

^{15;17;18;291} Differences in the prevalence of these conditions in this population

relative to those reported in the published literature could contribute to differences in study findings.

After excluding patients with a diagnosis of mental retardation, 69 percent of the population had at least one mental health diagnosis, with 32.1 percent having more than one diagnosis. While it is possible that antipsychotic therapy was inappropriately prescribed for patients, the absence of a mental health diagnosis for over 30 percent of this study population may be an artifact of coding practices rather than a statement that these patients did not actually have a mental health disorder. Schizophrenia and bipolar disorder were the most frequent indications for treatment; however, they accounted for only 32 percent of the study population (16.5 and 15.5%, respectively). This finding is consistent with national prescribing practices for antipsychotic therapy where ‘off-label’ prescribing has been widely reported.^{88;320;321}

Among the published retrospective studies in this field, approximately 50 percent restricted inclusion to patients with specific mental diagnoses, for example, patients with a diagnosis of schizophrenia,^{3;226;231;242;246;250;251} a mood disorder,²³⁸ a psychotic disorder^{236;237} or dementia.²⁵² The prospective CATIE trial limited inclusion to patients with chronic schizophrenia.²⁵⁴ Less than one-third of the retrospective trials permitting inclusion of any patient treated with an antipsychotic reported the prevalence of mental health diagnoses in the population.^{4;9;10;225;228-230;232-235;241;245;247-249} While the majority reported a non-significant association between mental health diagnosis and development of new-onset diabetes,^{10;228;230;233;236;238;239;242;246} others reported significant differences in risk based on diagnosis.^{237;240;241;244} Patient clinical characteristics, therefore, represent an important control variable when examining the association between antipsychotic use and the risk of new-onset diabetes. The importance of mental

health diagnosis will be further discussed in section 4.2.2, examining the pattern of antipsychotic prescribing according to treatment indication.

4.2.1.2.2 Hypertension

Hypertension is a known risk factor for diabetes.²²⁴ Overall, 24.9 percent of patients were identified as having hypertension on the basis of having a medical claim with an ICD-9 diagnosis for hypertension. The estimated prevalence of hypertension in the U.S. population is 15 percent, but is increased among minority races and in older adults.^{380;381} The baseline prevalence of hypertension in the CATIE trial, a population of younger patients with diagnosed schizophrenia, was 20 percent.²⁵⁴ Several of the published retrospective studies in this area included hypertension as a covariate in their analyses,^{10;228;241;247;250-252} with four studies reporting a significant increase in risk of new-onset diabetes for patients with comorbid hypertension after controlling for all other factors.^{10;241;247;251}

4.2.1.2.3 Dyslipidemia

Dyslipidemia (specifically high triglycerides and low HDL cholesterol) is a known risk factor for diabetes.²²⁴ In this study, 9.2 percent were defined as having dyslipidemia on the basis of a medical claim with an ICD-9 code for dyslipidemia, or a prescription for a lipid-lowering agent. The prevalence of dyslipidemia in the CATIE trial, as determined by laboratory testing at baseline was 14 percent.²⁵⁴ The difference in prevalence rates may relate to a number of factors including: under-detection of dyslipidemia in the Medicaid cohort; an increased detection of dyslipidemia in the CATIE trial because of baseline testing; and systematic differences in health-seeking behavior between patients who prospectively consent to inclusion in a clinical trial compared to the general population. The inclusion of dyslipidemia as a covariate in the published retrospective studies in this area was limited; however, several reported a

significant increase in risk of new-onset diabetes in patients with comorbid dyslipidemia after controlling for all other factors.^{228;239;247;250;251}

4.2.1.3 Medication Variables

Several classes of medications have the potential to increase the risk of diabetes and had the potential to confound this study.²⁰⁴ Prescriptions for a concomitant diabetogenic medication were redeemed by 26.2 percent of the population, with valproic acid and beta-blockers the most commonly used (9.4 and 6.3% of the population, respectively). Several published retrospective studies in this area controlled for use of other diabetogenic medications,^{3;226;229;231;232;235-240;245} with approximately half finding a significant increase in risk of new-onset diabetes associated with their use, after controlling for all other factors.^{226;232;236-238;240}

4.2.1.4 Summary

The demographic and clinical characteristics considered herein are important with regard to the epidemiology of diabetes. Differences were observed between this study cohort and those examined in published prospective and retrospective studies in this area. These differences may help explain any variability between the study findings.

4.2.2 Objective 2: Antipsychotic Utilization Patterns

The second objective of this study was to examine antipsychotic utilization patterns in the study cohort. Of interest were differences in treatment patterns that may confound the relationship between antipsychotic exposure and the development of diabetes. The choice of antipsychotic agent, doses used, duration of treatment and compliance with therapy will now be discussed relative to the available literature.

4.2.2.1 Choice of Agent

This study examined the use of antipsychotic monotherapy. The first identified antipsychotic agent was considered to be the index agent with the proviso that no other antipsychotic agent was dispensed in the preceding six months (180 days). The majority of patients (70.7%) received a second-generation antipsychotic as their index agent. Risperidone was the most frequently prescribed of these agents, accounting for approximately 60 percent of second-generation agent prescriptions, and 42.4 percent of all prescriptions. Other frequently prescribed agents were olanzapine (21.6%) and quetiapine (6.3%). Clozapine was infrequently prescribed (93 patients); and no patient received ziprasidone as index therapy.

These trends are consistent with national trends during the time period of this study (1997 to 2001). For example, data from the National Ambulatory Medical Care Surveys (NAMCS) indicated a decline in the use of first-generation antipsychotics from 40 percent of prescriptions in 1997 to 29 percent in 2000.³²¹ A similar trend has been noted in the Veterans Affairs Administration database.¹⁹ Likewise, in a study of national retail drug expenditures in 2001, 75 percent of the expenditure on antipsychotic agents was accounted for by olanzapine (45%) and risperidone (30%).³¹⁸

Four hypotheses (1a-d) were tested regarding the choice of antipsychotic agents. The study hypotheses and results of the associated statistical analyses are summarized in Table 3.32.

4.2.2.1.1 Age

When stratified according to patient age, the rate of prescribing of the various antipsychotic agents differed ($\chi^2 = 416.748$, $df=16$, $p<0.001$), and accordingly hypothesis 1a was rejected. Although used by 42.2 percent of the study cohort, risperidone was proportionately more frequently used by patients

aged 18 to 34 years (46.1 %) and patients aged 65 years or more (48.3%). This contrasted with the prescribing of olanzapine, which was less likely to be used at the extremes of age (16.7 and 18.7%, respectively, compared to 21.6% overall). This trend was consistent with that observed in the National Ambulatory Medical Care Survey (NAMCS).³²¹

Significant differences were also observed in the mean patient age for the different agents ($F = 85.83$, $df=4$, $p<0.001$). Compared to a population mean of 60.3 years (SD: 21.9), patient age ranged from 37.4 years (SD: 13.3) for patients treated with clozapine to 63.1 years (SD: 22.0) for patients treated with risperidone. Patients treated with olanzapine had a mean age of 57.3 years (SD: 21.6). Post-hoc analyses were significant ($p\leq 0.02$) for all comparisons, with the exception of that between recipients of quetiapine and recipients of the first-generation antipsychotics ($p=0.423$). As noted previously, this study did not limit inclusion to patients aged between 18 and 65 years. Not surprisingly then, regardless of the agent used, patients were older in this cohort than those enrolled in comparable prospective and retrospective studies.^{235-241;244;246-248;250;254}

Both the prevalence and incidence of diabetes are known to increase with increasing patient age.^{201;276} Differences in patient age according to the agent used could have important implications with regard to the relative risk of diabetes attributed to the various agents.

4.2.2.1.2 Gender

A significant relationship was noted between choice of index antipsychotic agent and patient gender ($\chi^2 = 416.748$, $df=16$, $p<0.001$). Risperidone and quetiapine were more commonly used in women, with first-generation antipsychotics, clozapine and olanzapine more commonly used in men. The second hypothesis (1b) was, therefore, rejected. Within each agent, the percentage of female recipients varied from 39.8 percent for clozapine to 71.2

percent for quetiapine, as compared to 65.7 percent for the overall population ($\chi^2 = 76.901$, $df=4$, $p<0.001$). The results of these evaluations must be considered in the context of the information presented in section 4.2.1.1, that is, that this study cohort had a higher percentage of females than comparable studies in the literature. Nationally, the highest incidence of diagnosed diabetes is among men aged 65-79 years, with 14.5 cases per 1,000 population reported in 2000, compared to 9.4 cases per 1,000 population among women of the same age.²⁷⁶ These results support the inclusion of patient gender as a control variable in analyses examining the relative risk of new-onset diabetes attributed to the various antipsychotic agents.

4.2.2.1.3 Race/Ethnicity

A significant relationship was noted between choice of index antipsychotic agent and patient race/ethnicity ($\chi^2 = 160.710$, $df=12$, $p<0.001$); hence, the third hypothesis (1c) was rejected. Compared to the cohort as a whole, Black patients were more likely to receive a first-generation antipsychotic, whereas Hispanic patients were more likely to receive risperidone. Both the prevalence and incidence of diabetes vary according to patient race/ethnicity, with higher rates reported among Blacks and Hispanics.^{201;276} As noted in section 4.2.1.1, the majority of studies published in this area did not report the race/ethnicity of the study population. Among studies reporting race/ethnicity, the percentage of White enrollees (range: 61-73%) was typically higher than in this cohort.^{227;228;235;239;249;251;252} The variation in prescribing according to race/ethnicity supports the inclusion of patient race/ethnicity as a control variable in analyses examining the relative risk of new-onset diabetes attributed to the various antipsychotic agents.

4.2.2.1.4 Primary Mental Health Diagnosis

Chi-square analysis indicated a significant relationship between choice of antipsychotic agent and primary mental health diagnosis ($\chi^2 = 845.046$, $df=20$, $p<0.001$). Hypothesis 1d was, therefore, rejected. The second-generation antipsychotics are indicated for the management of schizophrenia, and with the exception of clozapine, bipolar disorder.³⁶⁻⁴⁰ It is noteworthy, however, that at the time these data were collected (1997 to 2001), only olanzapine was licensed for use in bipolar disorder, having been licensed for management of acute bipolar mania in September 2000. After excluding patients with mental retardation, ‘off-label’ prescribing varied from 19.8 percent for patients receiving clozapine to 72.9 percent of risperidone recipients, while acknowledging that some of the patients without a mental health diagnosis may have had schizophrenia or bipolar disorder. This trend in ‘off-label’ prescribing is consistent with that observed in a number of national surveys of ambulatory antipsychotic use.^{320,321} As previously noted, patients with schizophrenia or bipolar disorder appear to be at an increased risk of diabetes, independent of antipsychotic use.^{13-15;17;18;291} This has not been consistently observed in studies that controlled for treatment indication while testing the association between antipsychotic use and new-onset diabetes.^{10;228;230;233;236-242;244;246} Regardless, differences in prescribing rates of the antipsychotic agents could serve to confound this relationship, hence the inclusion of primary mental health indication as a control variable in later analyses.

4.2.2.2 Antipsychotic Dose

The mean daily dose for each antipsychotic agent was inferred from information available on the quantity, strength and number of days supplied for each prescription. As outlined in section 3.1.3.3, calculated doses were examined for appropriateness and outliers excluded accordingly. In addition, a number of

sensitivity analyses were conducted in an attempt to ensure that the calculated doses were a reliable estimate of the prescribed mean daily antipsychotic dose for enrollees.

The calculated mean daily doses for the second-generation antipsychotics were: clozapine 426.21 milligrams (SD: 289.54); olanzapine 8.21 milligrams (SD: 5.80); quetiapine 128.09 milligrams (SD: 138.03); and risperidone 1.82 milligrams (SD: 1.67). With the exception of studies that limited enrollment to patients aged 60 years or older,^{234,252} the calculated mean daily antipsychotic doses for clozapine, olanzapine quetiapine and risperidone were lower than those noted in other retrospective studies in this area, most likely because of the greater diversity in treatment indications and the higher average age in this study.^{226;235;236;238-240;244;250}

There were eleven hypotheses (H_{2a-k}) regarding trends in antipsychotic dosing. Four hypotheses relating to the impact of age (2b and 2e) and treatment indication (2g and 2k) on the prescribing of clozapine and ziprasidone, respectively, were not tested due to the inadequate sample sizes. The study hypotheses and the results of the associated statistical analyses are summarized in Table 3.32.

4.2.2.2.1 Dose Classification

The mean daily doses for the second-generation antipsychotics were stratified as ‘low,’ ‘medium’ or ‘high dose’ based on consultation with a clinical expert. Patients treated with clozapine were omitted from these analyses due to the small sample size (N=93). Overall, 76.6 percent of patients were classified as receiving ‘low dose’ therapy, with only 5.5 percent classified as receiving ‘high dose’ therapy. Chi-square analysis indicated a significant relationship between antipsychotic dose classification and the specific antipsychotic agent used ($\chi^2 = 754.098$, $df=4$, $p<0.001$). Hypothesis 2a was, therefore, rejected. Among

olanzapine recipients, 11.8 percent received 'high dose' therapy (>15 milligrams daily) compared to 1.7 percent of quetiapine patients (>600 milligrams daily) and 2.8 percent of risperidone patients (>6 milligrams daily). Among quetiapine patients, 90.8 percent were classified as receiving 'low dose therapy' (≤ 300 milligrams daily), compared to 76.6 percent of olanzapine patients (≤ 10 milligrams daily) and 74.6 percent of risperidone patients (≤ 2 milligrams daily).

Lower doses of antipsychotics are typically recommended in elderly patients due to age-related differences in efficacy and tolerability of the antipsychotics. Accordingly, further analyses were conducted using a modified dose-stratification for patients aged 65 years or older. When limited to patients aged 18 to 65 years, and using the original dose stratification discussed above, 62.6 percent received 'high dose', 27.3 percent 'medium dose' and 10.0 percent 'low dose' therapy. In contrast, using the modified dose stratification for patients aged 65 years or older, 36.7 percent received 'low dose,' 45.5 percent 'medium dose,' and 17.7 percent 'high dose' therapy.

A number of studies published in this area have also classified treatment doses so as to facilitate dose-based comparisons between the antipsychotic agents.^{226;239} In a case-control study of schizophrenia patients enrolled in California Medicaid, Lambert et al. classified doses based on the empirical distribution of the actual doses and expert clinical knowledge. Although the dose stratifications differed somewhat from this study (e.g., less than 3 milligrams risperidone considered as 'low dose,' compared to doses less than 2 milligrams in this study), overall patients were less likely to be on low dose therapy (i.e., 17.2% for olanzapine, 34.4% for quetiapine and 20.0% for risperidone patients compared to 76.7%, 90.8% and 74.6%, respectively).²²⁶ Gianfrancesco et al. also stratified patients as receiving 'low,' 'medium' or 'high dose' therapy in a study involving patients with psychoses enrolled in Ohio Medicaid. This stratification

was based on the empirical distribution of the actual doses, adjusted for gender and age (child <18 years, or adult). Again, patients were less likely to be classified as receiving ‘low dose’ therapy with 27.1, 37.1 and 36.0 percent of olanzapine, quetiapine and risperidone recipients, respectively, receiving ‘low dose’ therapy.²³⁹ Both of these studies examined the impact of treatment dose on the incidence of diabetes as will be discussed later. Differences in the study findings may relate to differences in the antipsychotic doses employed.

4.2.2.2.2 Age

Overall, the mean daily antipsychotic doses prescribed to the study population were: olanzapine 8.21 milligrams (SD: 5.87); quetiapine 124.39 milligrams (SD: 136.77); and risperidone 1.80 milligrams (SD: 1.70). Patients treated with clozapine were excluded from this analysis due to the small sample size (N=93). Regardless of the agent, ANOVA and Kruskal-Wallis tests revealed significant differences ($p < 0.001$) in the mean daily dose according to patient age. All post-hoc comparisons between age strata were significant ($p \leq 0.002$) for patients treated with olanzapine and risperidone. A similar pattern was evident for quetiapine, with the exception of the comparison between patients aged 45 to 54 years and those aged 55 to 64 years ($p = 0.073$). Hypotheses 2c, 2d and 2e were, therefore, rejected.

Regardless of the agent, patients aged 65 years or older, received approximately 50 percent (range: 43.4% to 51.2%) of the dose prescribed to those aged less than 65 years. As noted previously, the calculated mean daily antipsychotic doses in this study were lower than those noted in other retrospective studies in this area.^{226;235;236;238-240;244;250} However, the doses used for patients aged 65 years or older in this study were very similar to those reported in studies that limited enrollment to patients aged 60 years or older.^{234;252} For example, Feldman et al. examined the incidence of new-onset

diabetes in patients aged 60 years or older treated with antipsychotic monotherapy. The reported mean daily doses were: olanzapine 5.1 milligrams (SD: 4.3); quetiapine 95.5 milligrams (SD: 83.4); and risperidone 1.2 milligrams (SD: 1.0).²³⁴ This compares to 5.4 milligrams (SD: 3.8), 76.5 milligrams (SD: 70.4), and 1.2 milligrams (SD: 0.9), respectively, for patients aged 65 years or older in this study. Similar dosing patterns were noted when comparing the doses used for patients aged less than 65 years in this study to the doses reported in studies that limited enrollment to patients aged less than 65 years,²⁵⁰ or had younger patient populations than this study.^{235;236;238;240;244} The similarity in dosing patterns between the studies serves to corroborate the inferred daily doses used in this study.

4.2.2.2.3 Primary Mental Health Diagnosis

The mean daily doses for the second-generation antipsychotics were examined according to the primary mental health indication for which they were presumed to be prescribed. As described in section 2.4.2.2.1, a hierarchical approach was taken when stratifying patients according to their mental health diagnoses. For example, a patient with diagnoses for schizophrenia, major depressive disorder and anxiety disorder, was classified as having schizophrenia in this study, with the other conditions considered to be comorbid to the primary diagnosis of schizophrenia. It was then presumed that antipsychotic therapy was prescribed for the primary condition. Patients with an ICD-9 code for mental retardation were excluded from this analysis due to the difficulty of making other mental health diagnoses in this population. As noted previously, hypotheses relating to clozapine (2g) and ziprasidone (2k) were not tested due to inadequate sample sizes. Regardless of the antipsychotic agent, when examined using ANOVA and Kruskal-Wallis tests, mean daily treatment doses varied

significantly ($p < 0.001$) according to the treatment indication. Hypotheses 2h (olanzapine), 2i (quetiapine) and 2j (risperidone) were, therefore, rejected.

Trends in the prescribing of the antipsychotic agents merit further discussion. Regardless of the agent, mean daily treatment doses declined in the following order: schizophrenia; bipolar disorder; no mental health diagnosis; non-psychotic disorder; psychotic disorder; with the lowest calculated doses prescribed to patients with dementia. Doses for schizophrenia and bipolar disorder differed significantly ($p \leq 0.005$) from each other, and from those used for each of the other indications. Additional analyses were conducted after stratifying the population into patients aged less than 65 years, and those aged 65 years or older and similar trends in prescribing were noted. With the exception of quetiapine prescribing in patients aged 65 years or older, antipsychotic doses differed significantly ($p < 0.001$) according to the treatment indication in both age strata. Regardless of age or agent, patients with schizophrenia were prescribed the highest doses. Of interest also was the comparison of treatment dose between the two age groups. Regardless of indication or agent, patients aged 65 years or older, received approximately 50 percent of that prescribed to their younger counterparts.

This additional information facilitates comparison with the published literature in this area, where many of the studies restricted eligibility based on age (< 65 years, or ≥ 65 years) or mental health diagnosis or both. Micca et al. examined the association between new-onset diabetes and use of olanzapine in patients with dementia aged 65 years or older. The modal dose of olanzapine was 4.87 milligrams, which is comparable to the mean daily dose of olanzapine (4.79 milligrams (SD: 2.92)) prescribed to patients with dementia aged 65 years or older, in this study.²⁵² Zhao et al. tested for antipsychotic-associated new-onset diabetes in a population of patients with diagnosed schizophrenia aged between

18 and 64 years who were enrolled in a private health care plan. The mean daily doses of olanzapine and risperidone were 9.96 milligrams and 3.39 milligrams, respectively, (standard deviations not reported).²⁵⁰ These were somewhat lower than the doses noted for the same cohort in this study (olanzapine 12.6 milligrams (SD: 6.70); risperidone 3.83 milligrams (SD: 2.34). A number of other studies, using data from private insurance plans, limited inclusion to patients with a diagnosis of a psychotic disorder or any mental health diagnosis. Although not limiting enrollment to patients less than 65 years, they were comprised primarily of younger patients (as reflected by the mean age) and were thus more comparable to the patients aged 65 years or less in this study. Doses for olanzapine and risperidone were comparable, if somewhat lower than those calculated for patients aged 65 years or less in this study.^{236;238;240;244} These differences may be explained by the difference in insurance coverage. Patients with mental health disorders who have private health insurance generally are less severely ill, or have been ill for a shorter period of time than patients receiving treatment through publicly-funded sources. This is exemplified by the CATIE trial, where although insurance coverage was not reported, 85 percent of these patients with moderate to severe chronic schizophrenia were unemployed, with 88 percent previously, or never married and, therefore, unlikely to be covered by private health insurance by virtue of their own, or a spouse's employment.²⁵⁴

While serving to corroborate the antipsychotic doses and the mental health stratifications used in this study, the results from these analyses highlight the differences between this study and the published literature in terms of the composition and treatment of the study populations. Failure to control for dose and treatment indication in a heterogeneous population such as this could obscure the relationship between antipsychotic use and the development of new-onset diabetes.

4.2.2.3 Duration of Treatment

The mean duration of treatment was 115.2 days (SD: 118.5), ranging from one day to 365 days (the maximum period of follow-up). A significant difference ($p < 0.001$) was observed according to the class of antipsychotic used. Patients treated with a second-generation antipsychotic remained on treatment for an average of 128.4 days (SD: 123.3) compared to 83.3 days (SD: 99.2) for patients treated with a first-generation antipsychotic. The duration of treatment also varied significantly ($p < 0.001$) within the second-generation agents, decreasing in the following order: quetiapine 135.0 days (SD: 126.6); olanzapine 133.7 days (SD: 125.0); and risperidone 125.3 days (SD: 121.8).

These trends were comparable to those observed in a number of the studies published in this area,^{234;241;243;250} although differences in the duration of treatment and comparative trends were also reported.^{236-240;246;248;249} The studies all differed in their interpretation of treatment discontinuation and the maximum possible duration of follow-up. Consistent with this study however, was the considerable interpatient variability as evidenced by the large standard deviations reported. Many of the studies controlled for duration of treatment when analyzing the association between antipsychotic use and development of new-onset diabetes,^{3;9;230;234-239;241;243;246;248;249} with a number reporting a significant association between increasing duration of treatment and onset of diabetes.^{237-239;241}

4.2.2.4 Compliance

Two measures of antipsychotic compliance were assessed in this study: adherence and persistence. A total of ten hypotheses (H_{3a-j}) were tested regarding trends in compliance, a summary of which is included in Table 3.32. While duration of therapy was frequently included as a covariate in retrospective studies examining the association between antipsychotic use and new-onset diabetes,

3;9;230;234-239;241;243;246;248;249 measures of compliance with therapy were rarely included.²²⁸ It was important to incorporate compliance as a surrogate measure of drug exposure as, to paraphrase the saying: “Drugs don’t work in patients who don’t take them;” it is equally probable that drugs won’t cause adverse effects in patients who don’t take them.

4.2.2.4.1 Adherence

Adherence to therapy was measured using the medication possession ratio (MPR). This is a widely used measure of treatment compliance in automated databases, with advantages including ease of calculation and interpretability. The MPR is typically calculated in one of two ways: using the interval between the first prescription and exhaustion of the last prescription refill, or using a defined period of follow-up (e.g., 365 days) as the denominator. An MPR of 0.8 or greater is frequently applied as a threshold for adherence, that is patients with an MPR of 0.8 or more are considered to be adherent with therapy, while those with an MPR less than 0.8 are considered non-adherent.³⁸² Using the former classification, the mean adherence to therapy in this study was 0.803 (SD: 0.266) with 59.4 percent classified as adherent with therapy, while for the latter (MPR_365 days), the mean adherence was 0.600 (SD: 0.316) with 34.6 percent considered adherent. These figures correspond with reports in the literature of adherence with antipsychotic therapy. In a study of antipsychotic adherence by patients with schizophrenia enrolled in Medicaid, 41 percent were considered adherent with therapy (MPR 0.80-1.10).³⁴⁵ Likewise, using data from the Veterans Affairs National Psychosis Registry, the mean adherence rate for patients with schizophrenia or schizoaffective disorder was 0.80 (SD: 0.33) with 60 percent of patients having an MPR of 0.80 or greater.³⁴¹

4.2.2.4.2 Persistence

The second measure of compliance used in this study was persistence with antipsychotic therapy. This is another widely used measure of treatment compliance in automated databases; however, studies vary in how persistence is calculated.³⁸² In this study, a patient was considered persistent with therapy if they refilled their prescription within a given grace-period of the previous prescription being exhausted. The grace period was calculated using 50 percent of the number of days in the previous prescription. This method of calculating persistence has been commonly used in the literature.³⁸² It was chosen in preference to another common method which uses defined grace-periods in days (typically 7-180 days), largely because of the requirement at the time that clozapine prescriptions be dispensed for a maximum of seven days.³⁶ The primary objective of this study was to estimate the incidence of diabetes associated with exposure to antipsychotic therapy. Using a set grace period (such as 30 days), a patient with medication available for at least 30 out of 60 days would be considered persistent with therapy, but equally a patient with medication available for only seven out of every 37 days would be considered persistent, reducing the specificity of this measure of drug exposure. The mean number of persistent days in the study was 128.7 days (SD: 120.2), with a median of 77 days. This measure will be discussed in greater detail in the next section examining trends in compliance.

4.2.2.4.3 Factors Affecting Compliance

As noted, a total of ten hypotheses (H_{3a-j}) were tested regarding trends in compliance. A summary of the hypotheses and the associated statistical analyses is included in Table 3.32. In each instance, factors affecting adherence to therapy were analyzed twice, once using an MPR calculated using the interval between the first prescription and exhaustion of the last prescription refill as the

denominator (MPR), and also as a sensitivity analysis using 365 days as the denominator (MPR_365). Unless specified otherwise it may be assumed that the results of the bivariate analyses were the same regardless of which measure of adherence (MPR or MPR_365) was used. As a second sensitivity analysis, persistence with therapy was recalculated using a 100 percent grace period, that is, a patient would be considered persistent with therapy if they obtained a refill of a 30-day prescription within 30 days of the first prescription being exhausted. Again, unless specified otherwise, it may be assumed that the results from the bivariate analyses were the same regardless of which measure of persistence was used.

4.2.2.4.3.1 Age

ANOVA and Kruskal-Wallis tests revealed significant differences in adherence ($p < 0.001$) and persistence ($p < 0.001$) with antipsychotic therapy according to patient age. Similar trends were noted on post-hoc analyses for both measures, that is, the highest level of compliance was noted for patients aged 65 years or older, with the lowest levels noted for patients aged between 18 and 34 years. Hypotheses 3a and 3b were, therefore, rejected.

This result is consistent with reports of decreased adherence to antipsychotic therapy among younger patients.^{341;345;347} Living status has also been associated with adherence, with lower rates reported in homeless patients and those living independently compared to those living with family or assisted living facilities.³⁴⁵ While housing status was not included in this dataset, it is probable that a higher proportion of elderly patients in this dataset were residing in nursing homes or assisted living facilities, not least because of the higher prevalence of dementia in this cohort. Medication administration tends to be supervised in these settings, increasing adherence with therapy and reducing the risk of self-discontinuation of therapy, ergo higher persistence rates.

4.2.2.4.3.2 Gender

As noted previously, adherence as measured by medication possession ratios were calculated to a treatment endpoint (MPR) and as a sensitivity analysis for a fixed 365-day follow-up period (MPR_365). Whereas by the former, a significant difference was noted in adherence according to patient gender (Mean MPR men: 0.791 (SD: 0.269); mean MPR women 0.808 (SD: 0.264) $p < 0.001$), no difference was noted for the latter (Mean MPR_365 men: 0.605 (SD: 0.316); mean MPR_365 women 0.597 (SD: 0.316) $p = 0.141$). While hypothesis 3c was rejected, it is unlikely that the observed difference in MPR for men and women (mean difference: 0.017) would be of any clinical significance. No difference was noted in persistence (0.653) with antipsychotic therapy according to patient gender. Accordingly, hypothesis 3d was accepted.

These results are consistent with reports in the published literature both for antipsychotics³⁴⁵ and other medications,^{383;384} that gender is not a significant predictor of adherence or persistence with antipsychotic therapy.

4.2.2.4.3.3 Race/Ethnicity

ANOVA and Kruskal-Wallis tests revealed significant differences in adherence ($p < 0.001$) and persistence ($p < 0.001$) with antipsychotic therapy according to patient race/ethnicity. Similar trends were noted on post-hoc analyses for both measures, that is, the highest level of compliance was noted for Whites and the lowest levels noted for Blacks. Hypotheses 3e and 3f were, therefore, rejected.

These results are consistent with published literature on compliance with antipsychotic therapy. Opolka et al. noted a significant association between ethnicity and adherence in a study using patients with schizophrenia or schizoaffective disorder enrolled in Texas Medicaid. As in this study, the lowest rates of adherence were noted for Blacks, followed by Hispanic patients with the

highest adherence among Whites.³⁴⁷ Likewise in a study of treatment adherence in patients with schizophrenia enrolled in California Medicaid, adherence was noted to be lowest among African Americans and Latinos, with higher rates among Non-Latino Whites, Asians and those in the ‘Other’ race/ethnicity group.³⁴⁵ Similar results have been reported by Valenstein et al. in a study of patients with schizophrenia using the Veterans Affairs National Psychoses Registry.³⁴¹

4.2.2.4.3.4 Primary Mental Health Diagnosis

ANOVA and Kruskal-Wallis tests revealed significant differences in adherence ($p < 0.001$) and persistence ($p < 0.001$) with antipsychotic therapy according to the primary mental health diagnosis. The highest rates of adherence and persistence were noted for patients with a diagnosis of dementia, with the lowest adherence and persistence rates noted in patients with schizophrenia and bipolar disorder, respectively. Hypotheses 3g and 3h were, therefore, rejected.

These results support an earlier theory that older patients with dementia are more likely to reside in nursing homes or assisted-living facilities, with greater opportunity for caregiver supervision and intervention, resulting in higher compliance with therapy. The mean MPR of 0.761 (SD: 0.259) for patients with schizophrenia is comparable to that noted in a study of a younger, less racially diverse cohort of patients with schizophrenia enrolled in the Veterans Affairs Health Care System (MPR: 0.80 (SD: 0.33)).³⁴¹ Likewise, comparable rates of adherence with therapy have been documented for psychoses, depression and bipolar disorder to those noted in this study.^{344;384} The long persistence with therapy (124.0 days (SD: 116.7)) observed for patients with non-psychotic disorders is at odds with clinical guidelines that recommend a short (range: one week to two months) duration of treatment for these conditions.¹¹ Similarly, for patients with dementia, guidelines suggest episodic, rather than continuous

therapy with antipsychotics, and accordingly a shorter persistence with therapy might have been expected here.¹¹

4.2.2.4.3.5 Antipsychotic Agent

After excluding patients treated with clozapine due to the small sample size, ANOVA and Kruskal-Wallis tests revealed significant differences in adherence ($p < 0.001$) and persistence ($p < 0.001$) with therapy according to the specific antipsychotic prescribed (olanzapine, quetiapine, risperidone or a first-generation agent). Regardless of the measure used, compliance was seen to decline in the following order: quetiapine, olanzapine, risperidone, with the lowest compliance rates noted for patients treated with a first-generation agent. Hypotheses 3i and 3j were, therefore, rejected.

Similar results were noted in a study of adherence to antipsychotic therapy among schizophrenia patients enrolled in Texas Medicaid. Opolka et al. noted the highest adherence with olanzapine, then risperidone with the lowest adherence among patients prescribed haloperidol, a first-generation antipsychotic.³⁴⁷ Using different measures of treatment adherence, Dolder et al. reported increased adherence with second-generation compared to first-generation antipsychotics after six ($p = 0.05$) and 12 months ($p = 0.11$) of treatment, in a small study of patients with psychosis enrolled in the Veterans Affairs Health Care Administration. However, aside from a significant difference in adherence between olanzapine and haloperidol ($p = 0.008$) at six-months, no other contrasts between the individual antipsychotics (haloperidol, perphenazine, olanzapine, quetiapine, risperidone) were significant.³⁴⁸

The results contrast with findings from a number of other studies. In a prospective study of compliance with antipsychotic therapy among patients with schizophrenia, levels of adherence and persistence with therapy were consistently and significantly higher for patients treated with olanzapine (MPR: 0.75;

persistence: 259 days) than for patients treated with risperidone (MPR: 0.69; persistence 237 days) or quetiapine (MPR: 0.61; persistence 212 days).³⁴⁹ In the CATIE trial, the time to discontinuation of therapy (which approximates persistence with therapy) decreased in the order: olanzapine, perphenazine (a first-generation antipsychotic), risperidone, quetiapine, with the shortest time to treatment discontinuation in those treated with ziprasidone.²⁵⁴ It is important to remember that clinical guidelines recommend life-long antipsychotic therapy for patients with schizophrenia and shorter periods of treatment (range: one week to six months), including the use of episodic rather than continuous therapy, for patients with other mental health diagnoses.¹¹ As the prescribing of the various antipsychotics varied according to the treatment indication in this study, it is possible that the observed differences in persistence rates reflect use of practice guidelines rather than necessarily differences in tolerability of the antipsychotic agents.

The differences observed between the studies may relate to differences between the study populations, or to differences in the measures of compliance used. Regardless, it is notable that compliance with antipsychotic therapy is low overall, and that it may vary according to the demographic and clinical characteristics of the population.

4.2.2.5 Summary

Significant differences were noted in the patterns of prescribing and compliance with antipsychotic therapy according to demographic and clinical variables. Failure to control for these differences could confound any association between the use of individual antipsychotic agents and the risk of new-onset diabetes. Differences in patterns of antipsychotic utilization in this study cohort relative to those in related prospective and retrospective studies may help to explain variability in the incidence and relative risk of diabetes reported.

4.2.3 Objective 3: Prevalence of Diabetes

In phase II of this study, the primary dependent variable was the prevalence of diabetes at baseline. Patients were screened for diabetes, as indicated by a medical claim with an ICD-9 code for diabetes or a prescription claim for insulin, an insulin-sensitizing agent or a glucose-lowering agent in the 180 days preceding the index prescription claim. Cases of diabetes noted in the first seven days of antipsychotic treatment were considered prevalent cases and were included in this analysis. This may have resulted in a misclassification of some incident cases, as cases of new-onset diabetes have been reported to occur as early as four to five days after initiating antipsychotic treatment.^{185;200} Patients with a history of diabetes but without a medical or pharmacy claim for same during the 180-day pre-screening period may also have been misclassified. The criteria for the diagnosis of diabetes changed slightly in July 1997, from a fasting plasma glucose level $\geq 140\text{mg/dL}$ to $\geq 126\text{mg/dL}$. It is possible that between January and July 1997, a small number of cases of prevalent diabetes may not have been included, only later to be misclassified as new-onset cases on the basis of the revised criteria. Patients in this study (particularly older patients) may have been dual-eligible for Medicaid and Medicare benefits. No medical claims data were available from Medicare, with the result that, again, prevalent cases of diabetes may have been underestimated in the study. Clearly, the prevalent cases of diabetes noted here are limited to patients with diagnosed diabetes. In 2002, it was estimated that five million (29%) of a possible 13 million patients with diabetes in the U.S. were undiagnosed.²²⁴ It is possible that the prevalence of diagnosed diabetes in this study is similarly underestimated.

The prevalence of diabetes in the study population was 16.9 percent. This is considerably higher than the estimated prevalence of diagnosed diabetes of 5.3 percent in the U.S. adult population.²²⁴ This figure also contrasts with an

estimated prevalence of diabetes of 10.7 percent among adults enrolled in Texas Medicaid in 2002. (Data on file, Texas Department of Health and Human Services, obtained 10/15/2004) The prevalence is also comparatively higher than that noted in the CATIE study (11.0%), that is, among a younger, primarily male, chronic schizophrenia cohort.²⁵⁴ Consistent with the well-documented epidemiology of diabetes, significant differences were seen in the prevalence of diabetes according to patient age (higher among older patients), and race/ethnicity (higher among Black and Hispanic patients compared to Whites).²²⁴ The prevalence was noted to be higher among women than men, possibly because of the higher percentages of older women in the study population. The majority of patients (85%) were captured by a pharmacy claim, with 49 percent captured by a medical claim, or a combination thereof. Studies that restricted the detection of diabetes to patients with a medical claim only^{225;231;242;244} or a prescription claim only^{9;227;232;234;240;245;247;248} clearly risked misclassifying prevalent cases. Nondifferential disease misclassification at baseline has been shown to bias incidence ratios away from the null, particularly in diseases where the prevalence at baseline is high relative to the incidence of the disease.³⁸⁵

The prevalence of diabetes at baseline varied significantly ($p < 0.001$) according to the index agent prescribed. Patients with prevalent diabetes were least likely to be prescribed a first-generation antipsychotic (14.8 %) and most likely to be prescribed risperidone (19.0%), assuming the physician prescribing the antipsychotic was aware the patient had established diabetes. As the data from this study were from 1997 to 2001, they predated both the expert panel recommendations regarding choice of antipsychotics in patients with multiple risk factors for diabetes,²⁶¹ and publication of the results from various prospective²⁵⁴ and retrospective studies in this area.^{3;4;9;10} It is possible that

physicians were cautious about prescribing olanzapine to patients with prevalent diabetes due to concerns regarding additional weight gain. It is also possible though, that this pattern of prescribing was due to age, and indication-related differences in prescribing patterns noted in sections 4.2.2.1.1 and 4.2.2.1.4, rather than concerns regarding the potential for metabolic effects associated with the various antipsychotic agents.

The prevalence of diabetes varied significantly when stratified according to primary mental health diagnosis. After excluding patients with mental retardation, the unadjusted prevalence of diabetes ranged from 12.4 percent among patients with schizophrenia to 20.6 percent among patients with a psychotic disorder ($p < 0.001$). Multivariate logistic regression analysis showed that even after controlling for differences in demographic and clinical risk factors for diabetes, mental health diagnosis remained significantly associated with the prevalence of diabetes ($p = 0.006$). Accordingly, hypothesis 4a was rejected. Compared to patients with schizophrenia, the odds of prevalent diabetes were increased by 26 percent for patients with bipolar disorder ($p = 0.003$), 25.3 percent for patients with a non-psychotic disorder ($p = 0.006$) and 25.0 percent for patients with no mental health diagnosis ($p = 0.003$). These results are not inconsistent with published literature, suggesting a higher prevalence of diabetes in patients with mental disorders including schizophrenia and bipolar disorder when compared to the general population.^{13-15;17;18;291} It is possible that the difference in prevalence between the mental health categories reflects a difference in access to care by the various patient groups, as opposed to true differences in the risk of diabetes. It is well documented that, despite frequent contact with health services, patients with serious mental illness do not necessarily receive appropriate primary healthcare.^{313;314} In addition, there are reports of provider difficulties in performing and receiving reimbursement for diagnostic tests in ambulatory

psychiatry clinics. These factors may have combined to reduce the detection of prevalent diabetes in patients with schizophrenia.

Consistent with the standard literature, several known risk factors for diabetes were shown to be significantly associated with prevalent diabetes that is, increasing age, minority race/ethnicity, hypertension and dyslipidemia.²²⁴ Somewhat curious was the negative association between use of other diabetogenic medications and the odds of prevalent diabetes. This may have related to variability in the risk of diabetes associated with the different medications in this group. Alternatively, as the risk of diabetes has been well established with these agents, it is possible that clinicians avoided prescribing these medications to patients with known diabetes for fear of exacerbating their condition.

In summary, the baseline prevalence of diabetes was higher in the study population compared to both the general U.S. population and to the general adult Texas Medicaid population. A significant association was noted between mental health diagnosis and the prevalence of diabetes, although the absolute difference in risk between the various diagnoses was relatively small. Use of a six-month prescreening period for diabetes and consideration of both medical and pharmacy claims for diabetes may have diminished the misclassification of prevalent cases at baseline.

4.2.4 Objective 4: Incidence of Diabetes

In phase III, the primary dependent variable was the incidence of diabetes as detected by a new medical claim with an ICD-9 code for diabetes, or a new prescription for insulin, an insulin-sensitizing agent or a glucose-lowering agent. The incidence of diabetes in this study population was 2.37 percent, with 59 percent of new cases identified by a pharmacy claim and 75 percent of cases identified by a new medical claim (35.5% identified by both pharmacy and

medical claims). This contrasted with the pattern of identification of prevalent cases where more patients were detected on the basis of a pharmacy claim, or combination of a pharmacy and medical claim. This result is not inconsistent with patterns of medical coding in clinician practice, where chronic conditions are relegated to secondary diagnoses, or possibly omitted altogether. It is reasonable that more patients were classified as having new-onset diabetes on the basis of having a new medical claim, or a combination of medical and pharmacy claims for diabetes, as patients may have sought medical care when symptoms of diabetes manifested. This pattern is consistent with the typical management of type 2 diabetes where patients may initially be managed by lifestyle modifications alone. In particular, if an iatrogenic cause is suspected, a ‘wait and see’ approach may be adopted to see if the hyperglycemia reverses with withdrawal of the suspected agent. Regardless, this result again serves to highlight the need to include both medical and pharmacy claims when using surrogate markers to identify cases of diabetes.

The incidence of diabetes in this study was higher than that reported for the U.S. general population. In 2001, the age-adjusted incidence of diabetes was 0.29 percent for those aged 18 to 44 years, 1.14 percent for those aged between 45 and 64 years, and 1.18 percent for those age 65 and 79 years.²⁷⁶ This contrasts with rates of 1.26 percent, 3.33 percent and 2.80 percent, respectively, in this study population (noting that there was no upper age limit in this study). Medicaid is over-represented by minorities and those with a lower socioeconomic status, both of which have been associated with an increased risk of diabetes.^{386,387} These demographic differences may account for the discrepancy between the incidence rates.

The unadjusted incidence of diabetes in the population varied significantly according to age ($p<0.001$), gender ($p<0.001$) and race/ethnicity

($p < 0.001$) when examined using Chi-square analysis. These results were consistent with those observed in the prevalence study, and with the exception of gender, with the known epidemiology of diabetes in the U.S. population.²⁷⁶ The higher unadjusted incidence of diabetes in women compared to men (2.7% versus 1.7%), may have resulted from an over-representation of older women in this cohort. However, while female gender is not a risk factor for diabetes, the impact of low socioeconomic status is greater among women regardless of ethnicity, with higher rates of diabetes noted in poor women.³⁸⁶

The unadjusted incidence of diabetes did not differ significantly according to treatment indication ($p = 0.051$). The trend in rates was similar to that noted in the prevalence study, that is, a trend towards fewer cases of diabetes among patients with schizophrenia or no mental health diagnosis. As noted previously, this trend may reflect differences in the access to primary care and monitoring between diagnostic groups. Chi-square analysis did reveal a significant association between the index antipsychotic agent and the unadjusted incidence of diabetes. While higher rates of diabetes were noted for patients treated with risperidone (2.8%) and olanzapine (2.5%), these results need to be considered in the context of earlier bivariate analyses regarding age and indication-related prescribing of the antipsychotic agents. The association between antipsychotic agent and incidence of diabetes will be discussed further in section 4.2.4.2.

4.2.4.1 Time to Development of Diabetes

The mean time to development of diabetes (using the date of the first medical or pharmacy claim for diabetes as a proxy for the date of onset of diabetes) was 95.9 days (SD: 85.1) with a median time to onset of 62.5 days. This varied by agent, ranging from a median of 51.0 days for quetiapine to 73.0 days for olanzapine. Data were positively skewed. This is not inconsistent with

reports in the literature. Specifically, among the published case reports (Appendix A, Table 2.4), more than 50 percent of cases occurred within three months of initiating antipsychotic therapy with over two-thirds (69.7%) reported within six months of initiating therapy. In this study, 59.9 percent of cases occurred within three months, 83.8 percent within six months, and 93.5 percent within nine months of commencing therapy.

Two Cox regression models were developed to test hypotheses 5a and 5b regarding the time to occurrence of diabetes. The same demographic and clinical variables were entered into both models. The models differed in the medication variables included. Model 1, compared the time to onset of diabetes between first- and second-generation antipsychotics. Model 2, compared between the second-generation antipsychotics. This model also controlled for the dose of the second-generation antipsychotic used. Both models were significantly different from the null model as indicated by the Model Chi-squares ($\chi^2 = 173.699$, $df=18$, $p<0.001$ and $\chi^2 = 132.115$, $df=21$, $p<0.001$, respectively). Due to inadequate sample size, clozapine and ziprasidone were not included in this analysis. Hypotheses 5a and 5b and the results of the associated statistical analyses are summarized in Table 3.32.

4.2.4.1 1 Class of Antipsychotic

Overall, 14,124 patients were included in this analysis, of whom 381 (2.70%) developed diabetes. No difference was noted in the unadjusted ($p\geq 0.071$) or adjusted ($p=0.484$) time to occurrence of diabetes between patients treated with first or second-generation antipsychotics. Hypothesis 5a was, therefore, accepted.

Covariates in the Cox proportional hazards regression model that were significantly associated with an increased time to development of diabetes were female gender, Black or Hispanic race/ethnicity, increasing age, and a diagnosis

of comorbid hypertension or dyslipidemia. These results are somewhat counterintuitive. As noted previously, risk factors for the development of diabetes include minority race, increasing age and a history of hypertension or dyslipidemia.²²⁴ Accordingly, one might expect clinicians to screen for diabetes more frequently in these patients, ergo an apparent quicker time to onset of diabetes. It is noteworthy, however, that disparity in both the access to, and quality of medical care for ethnic minorities has been documented – factors which could delay the time to detection of diabetes.³⁸⁷ Access and quality of preventative care has also noted to be lower among women, which may explain the apparent increase in time to development of diabetes in this group.³⁸⁶

Two covariates were associated with a shorter time to onset of diabetes – adherence to antipsychotic therapy (compared to non-adherence) and use of a concomitant diabetogenic medication. The former may be due to an increased risk of diabetes associated with increased exposure to antipsychotic medications. It is also plausible that differences in health-seeking behavior by adherent patients, with possible greater contact with physician services and more opportunities for the detection of diabetes may explain the apparent earlier time to onset in these patients. Regarding the latter, use of additional medications known to increase the risk of diabetes may hasten the time to onset, or time to screening and detection of diabetes in these patients.

4.2.4.1 2 Type of Second-Generation Antipsychotic

Overall, 9,799 patients were included in this analysis, of whom 301 (3.07%) developed diabetes. No difference was noted in the unadjusted ($p \geq 0.590$) or adjusted ($p = 0.278$) time to occurrence of diabetes between patients treated with the second-generation antipsychotics olanzapine, quetiapine or risperidone. Hypothesis 5b was, therefore, accepted.

Consistent with Model 1, differences in the time to onset of diabetes were noted according to patient race/ethnicity, history of hypertension or dyslipidemia, level of adherence with antipsychotic therapy and use of concomitant diabetogenic medications. While age and gender were no longer significantly associated with the outcome, the trend towards an increased time to development of diabetes with increasing age and female gender were again observed.

After adjusting for all other covariates, no association was noted between the dose of antipsychotic prescribed and the time to development of diabetes, supporting a hypothesis that the time to development of diabetes is not a dose-related phenomenon. The size of the confidence intervals associated with the parameter estimates indicates considerable variability in the data. The limited numbers of patients categorized as receiving high-dose therapy may have reduced the power of the study to detect a dose-response relationship, increasing the risk of a Type I error. The relationship between antipsychotic dose and time to onset of diabetes has not been discussed in the published literature in this area so it is difficult to draw further inferences from this result.

4.2.4.1.3 Summary

As noted previously, a surrogate marker was used in this study for this variable, that is, time to detection (as identified by a pharmacy or a medical claim for diabetes) versus actual time to development of diabetes. It is noteworthy that many patients may have diabetes for several years before first being diagnosed with the condition.²⁰⁴ The association between class and type of antipsychotic and time to development of diabetes was examined because of published case reports indicating rapid-onset diabetes (25% of cases occurring within four weeks of initiating antipsychotic therapy) which could be severe in nature (31 percent presenting in hyperglycemic crisis) associated with use of the second-generation antipsychotics, (Table 1.5) and more commonly, clozapine and

olanzapine. In this study, no difference in the time to onset of diabetes was noted between antipsychotic classes (first or second-generation) or between the specific second-generation agents.

4.2.4.2 Incidence of Diabetes – Contributing Factors

The potential for several variables to influence the incidence of diabetes in this cohort were investigated in detail using multivariate logistic regression analyses. Three study models were developed, each of which included the same demographic and clinical variables. Model 1 was used to test the hypothesis that the incidence of diabetes did not differ based on the class of antipsychotic agent, while controlling for all other variables. Model 2 was used to test the hypothesis that the incidence of diabetes did not differ according to the specific second-generation agent used, while controlling for all other variables. Additional variables included in this model were antipsychotic dose (stratified as ‘low,’ ‘medium’ or ‘high’) and compliance (as measured by adherence and persistence) with therapy. Six of a planned ten hypotheses were tested using Model 3, that is, that the incidence of diabetes did not differ according to the dose or primary mental health diagnosis for each of the individual second-generation antipsychotic agents (olanzapine, quetiapine, risperidone) while controlling for all other variables. Due to inadequate sample size, hypotheses 7a, 7e, 8a and 8e relating to dose and treatment indication for clozapine and ziprasidone patients, respectively, were not tested. This model controlled for the dose of the individual antipsychotic (as a continuous variable). All three models differed significantly from the null model as indicated by the Model Chi-square values ($p \leq 0.046$). Multicollinearity was excluded as a threat in an examination of the correlation values between the independent variables.

4.2.4.2.1 *Class of Antipsychotic*

Multivariate logistic regression analysis showed a non-significant ($p=0.193$) increase in the odds of new-onset diabetes of 21.6 percent for patients treated with a second versus a first-generation antipsychotic, after controlling for all other variables. Hypothesis 6a was, therefore, accepted.

This result is consistent with reports from the published literature in this area. Of nine studies that compared second-generation agents as a class to first-generation antipsychotic agents,^{3;4;228;229;234;241;246;247;250} eight reported an increase in the odds of diabetes with the second-generation agents (range: 1.1 to 2.6),^{3;4;228;229;234;241;246;250} with six reporting odds ratios less than 1.6.^{3;228;229;234;241;246} Only two studies reported a statistical difference in risk.^{4;246} Ollendorf et al. reported an increased odds of new-onset diabetes of 17.2 percent (95% CI: 1.061 to 1.130) with second-generation therapy in a study of patients with schizophrenia enrolled in private health care plans in the U.S.²⁴⁶ Likewise, Kwong et al. reported a significant increase in the odds of diabetes (OR: 2.6 (95% CI: 1.3 to 5.3) with second versus first-generation antipsychotic therapy in a study of antipsychotic recipients enrolled in the U.K General Practice Research Database. The number of patients prescribed a second-generation agent was small ($N=2,550$) relative to the number receiving a first-generation agent ($N=43,561$). Covariates included in the regression model were limited to age, gender and the presence or absence of obesity. Published in 2002, it is possible that the recipients of second-generation agents were systematically different from those receiving first-generation agents, and from those enrolled in this study.⁴ In the best known prospective study published in this area, the CATIE study, the time to treatment discontinuation due to intolerable side effects did not differ between the individual agents: olanzapine, risperidone, quetiapine, ziprasidone and the first-generation agent, perphenazine. It is notable however, that

olanzapine was associated with greater increases in weight ($p<0.001$) and glycosylated hemoglobin ($p<0.01$), but not mean serum glucose levels ($p=0.59$) compared to the other agents.²⁵⁴

Covariates that were significantly associated with an increased risk of diabetes included: age (increased with increasing age); female gender; race/ethnicity (increased risk for Black and Hispanic patients compared to Whites); comorbid hypertension or dyslipidemia. These findings are consistent with the known epidemiology of diabetes.²²⁴ Primary mental health diagnosis was not associated with the outcome ($p=0.403$). Compared to patients with schizophrenia, the odds of diabetes were increased for all diagnostic categories including those with no mental health diagnosis, although none of these comparisons were statistically significant. This is not inconsistent with the literature published on this topic. While patients with schizophrenia or bipolar disorder appear to have an increased risk of diabetes compared to the general population,^{13-15;17;18;291} reports also indicate an increase risk of diabetes in patients with depression.²⁹⁵⁻²⁹⁷ These studies did not compare the relative risk of diabetes among patients with mental health disorders. As noted previously, differences in healthcare utilization and access to medical monitoring may have led to an under-detection of diabetes in patients with schizophrenia reducing the apparent odds of diabetes associated with this condition.

The impact of compliance with antipsychotic therapy on the odds of diabetes in this analysis merits discussion. Two measures of compliance were included: adherence and persistence. The odds of new-onset diabetes decreased with increasing persistence with therapy. This finding is not unexpected given that published case reports and case series suggest that the majority of cases of diabetes associated with antipsychotic therapy occur early in the course of treatment. Patients who do not develop diabetes during the initial phase of

treatment may lack the diathesis to do so. Persistence with therapy was synonymous with duration of therapy in this study, except that compliance measures were limited to patients filling more than one prescription. Many of the studies in this area included duration of treatment as a covariate when analyzing the association between antipsychotic use and development of new-onset diabetes.^{3;9;230;234-239;241;243;246;248;249} Four reported a significant association between increasing duration of treatment and onset of diabetes,^{237-239;241} and while the magnitude of the increase in risk was small (OR range: 1.067-1.128) these results contrast with the findings of this study. As a sensitivity analysis, the analysis was repeated using persistence with therapy calculated using a 100 percent grace period between prescriptions with no difference in the final outcome.

Assuming that the risk of diabetes is increased with any, compared to no antipsychotic therapy, it is intuitive that the risk of diabetes would increase with increasing level of exposure to therapy. It is, therefore, reasonable then that the odds of new-onset diabetes increased for adherent patients (medication possession ratio (MPR) $\geq 80\%$) compared to non-adherent patients (MPR $< 80\%$). What is questionable is the magnitude of the increase in risk in this analysis (OR: 3.889, 95% CI: 2.999-5.044). This may represent an artifact of how adherence is calculated. As noted previously, among published case reports of diabetes associated with antipsychotic therapy, over 50 percent occurred within three months, with over two-thirds of cases occurring within six months of initiating therapy (Table 1.5, Appendix A). In contrast, adherence with therapy tends to decline with increasing duration of therapy. In this study, while each patient was followed for a maximum of one year, data were censored once a study endpoint occurred resulting in different lengths of patient follow-up. This potentially exaggerated the impact of treatment adherence, appearing higher for

patients with a short period of follow-up. Previous hypothesis testing in section 4.2.2.4 had indicated that trends in adherence were consistent regardless of the assessment period. To circumvent issues arising from variable periods of follow-up, adherence over a 365-day period was used as the covariate in the regression analysis. Several sensitivity analyses were conducted where adherence to therapy was included as a continuous variable, as a measure of adherence to a study endpoint only, substituting duration of therapy (that is, including patients who redeemed only one prescription), and using the final day on which a drug was available in lieu of adherence over 365 days. Regardless of the analysis, the net result was a failure to reject the null hypothesis, that the incidence of diabetes differs according to the class of antipsychotic used. What did vary was the estimate of risk associated with increasing adherence to therapy (e.g., odds ratios greater than 100 for adherent versus non-adherent patients). While the impact of treatment adherence may still be exaggerated using an intent-to-treat approach, the resulting odds ratio is more credible.

In summary, the findings of this study concur with published studies in this area that as a class, while the risk of diabetes may be increased with second-generation relative to first-generation antipsychotic agents, the magnitude of the increase is small, and typically not statistically significant.

4.2.4.2.2 Type of Second-Generation Antipsychotic

Using multivariate logistic regression analysis, a decrease in the odds of new-onset diabetes were noted with olanzapine (12.1%) and quetiapine (31.7%) compared to risperidone, after controlling for all other variables. These differences were not statistically significant ($p=0.397$ and $p=0.135$, respectively). Hypothesis 6b was, therefore, accepted.

As previously reported, prescribing of the second-generation antipsychotics varied according to patient age, gender, race/ethnicity and primary

mental health diagnosis. While these were included as covariates in the regression analysis, the study did not control for potential differences in access to medical monitoring for patients in the different mental health categories. This may have confounded the study findings, leading to an apparent increase in the odds of diabetes for patients prescribed risperidone – an agent that was preferentially prescribed to older patients with dementia. Also noted previously, it is possible that new-onset cases of diabetes were missed in patients that were dual-eligible for both Medicaid and Medicare, as the Medicare medical claims were not included in this study. This has particular implications for patients prescribed risperidone, the majority of whom were older and more likely to be dual-eligible for benefits, possibly reducing the apparent risk of diabetes in patients prescribed risperidone. The use of prescription claims data in addition to medical claims to identify new-onset cases of diabetes may have negated the possibility of such misclassification bias in this study.

Several retrospective studies have examined the relative risk of diabetes associated with the second-generation antipsychotics with variable findings. Consistent with this study, quetiapine has been associated with a comparable or lower risk of diabetes compared to risperidone.^{232;247;248} Etminan et al. reported ‘comparable risk’ between the two agents – the unadjusted risk of diabetes was 0.68 for quetiapine compared to risperidone.²³² Sacchetti et al. noted ‘no significant comparison’ between any of the second-generation agents, including between quetiapine and risperidone.²⁴⁸ Finally, Ostbye et al. reported a relative risk of diabetes of 0.66 (95% CI: 0.28-1.57) for quetiapine compared to risperidone.²⁴⁷

The relative risk of diabetes between olanzapine and risperidone is more contentious. Six of fourteen published retrospective studies reported a comparable or lower relative risk of diabetes with olanzapine compared to

risperidone (RR: 0.3–1.0),^{9;232;241;246;248;250} while eight studies reported an increased relative risk of diabetes with olanzapine (RR: 1.2–4.2),^{229;230;235;236;238;245;247;249} with the majority of studies reporting relative risks between 0.79 and 1.37.^{9;230;232;235;241;245-249} Of note, statistical significance was reported in only five studies, that is, in four of the studies reporting an increase in risk^{230;235;236;238} and in one study reporting a decrease in risk.²⁵⁰ The reliability of some of the results may be questioned. Whereas, Gianfrancesco et al. reported relative risks of diabetes of 3.53 (95% CI: 1.620-5.934) and 4.189 (95% CI: 2.102-8.827) for olanzapine compared to risperidone, these results were derived by extrapolating the odds of diabetes compared to untreated patients at one month to a 12-month exposure and then transforming the effect sizes so that a comparison could be made between the two agents.^{236;238}

This result compares to that noted in the CATIE study, which examined safety and tolerability measures as secondary goals. This study noted no significant difference in the time to treatment discontinuation due to intolerable side effects between the individual agents: olanzapine, risperidone, quetiapine, ziprasidone, and the first-generation agent, perphenazine. It is worth noting however, that olanzapine was associated with greater increases in weight ($p<0.001$) and glycosylated hemoglobin ($p<0.01$), but not mean serum glucose levels ($p=0.59$), compared to the other agents. For example, the mean exposure-adjusted difference in blood glucose from baseline was 13.7 ± 2.5 milligrams per deciliter for olanzapine and 6.6 ± 2.5 for risperidone, a net mean difference of 7.1 milligrams per deciliter. The net mean difference in glycosylated hemoglobin between the two agents was 0.29 percent, which would correspond with a net difference in mean serum glucose levels of approximately ten milligrams per deciliter over a three-month period.²⁵⁴

Antipsychotic dose was not significantly associated with the outcome. Compared to patients stratified as receiving ‘low’ dose therapy, a non-significant decrease in the odds of diabetes (25.4%) was seen with ‘medium’ dose therapy, whereas ‘high’ dose therapy was associated with a non-significant increase in the odds of diabetes of 15.9 percent. It is possible that the small number of cases among patients receiving high-dose therapy may have reduced the power of the study to detect an effect, increasing the risk of a type I error.

There is limited information on the association between antipsychotic dose and development of new-onset of diabetes in the literature. Gianfrancesco et al. reported a 10 to 25 percent increase in the risk of diabetes with medium or high-dose antipsychotic (first- or second-generation) therapy compared to no or low-dose therapy in a study of Ohio Medicaid enrollees with schizophrenia, bipolar disorder or major depressive disorder. This result is difficult to interpret. The comparator group included patients not receiving antipsychotic therapy. As there is a general consensus that the risk of new-onset diabetes is increased with first or second-generation antipsychotic therapy compared to no therapy, the significance of the dose related-effect proposed in this study becomes questionable.²³⁹

In a study of patients with schizophrenia enrolled in California Medicaid, Lambert et al. reported no association between antipsychotic dose (compared to any dose of a first-generation agent) and risk of diabetes for clozapine, olanzapine, quetiapine or risperidone using 12 or 24-week exposure windows. The possible dose-response for olanzapine found by Lambert et al. using a 52-week exposure window is not refuted by this study as the majority of patients in this study did not remain on treatment for 52 weeks. The difference between the two studies may alternatively be explained by the difference in patterns of antipsychotic prescribing. For example, 36.8 percent of enrollees in the

California Medicaid study received doses greater than 12.5 milligrams of olanzapine, compared to 11.5 percent with doses between 10 and 15 milligrams and 11.6 percent with doses greater than 15 milligrams in the Texas Medicaid; cohort, that is, there was a more pronounced dosing curve in the former.²²⁶

Consistent with earlier analyses, comorbid hypertension or dyslipidemia were significantly associated with the outcome. While no longer statistically significant, the trend towards an increased risk of diabetes with increasing age, female gender and Black or Hispanic race/ethnicity compared to Whites was again observed. As with Model 1, adherence with therapy was associated with a significant increase in the odds of diabetes, while increasing persistence was associated with a small, but statistically significant decrease in the odds of diabetes. Again, mimicking Model 1, the use of concomitant diabetogenic medications was paradoxically associated with a decrease (albeit non-significant) in the odds of new-onset diabetes. Likewise, while primary mental health diagnosis was not associated with the outcome, a trend toward an increase in the odds of diabetes for all mental health strata compared to schizophrenia was observed.

In summary, this study corroborates the findings of previous retrospective studies regarding the relative risk of diabetes between quetiapine and risperidone. While the non-significant reduction in risk with olanzapine compared to risperidone contrasts with the findings of several studies, it is noteworthy that the magnitude of the risk difference was typically small between the studies, with few reporting a significant difference in risk.

4.2.4.2.3 Antipsychotic Dose

The association between antipsychotic dose and the incidence of diabetes was examined individually for the second-generation antipsychotic agents (olanzapine, quetiapine and risperidone) using Model 3. The hypothesis testing

and statistical results are summarized in Table 3.32. As noted previously, hypotheses 7a and 7e relating to clozapine and ziprasidone, respectively, were not tested due to inadequate sample sizes.

4.2.4.2.3.1 Olanzapine

A total of 74 cases of diabetes (2.9%) were noted in the cohort of 2,521 patients included in this analysis. Using multivariate logistic regression analysis to control for other variables, each one milligram increase in olanzapine dose was associated with a 1.9 percent increase in the odds of diabetes. This difference was not however statistically significant ($p=0.995$). Trends in the odds of diabetes for all other covariates were consistent with those discussed in previous analyses. Hypothesis 7b was, therefore, accepted. The small number of cases of diabetes relative to the number of independent variables in the analysis may have increased the risk of a type I error in this analysis, limiting the interpretability of this result.

As noted previously, literature on a dose-related effect of olanzapine is sparse, and the results conflicting. While Buse et al. reported no dose-response with olanzapine,⁹ Lambert et al. reported a possible dose-response after 52-weeks exposure when compared to any dose of a first-generation antipsychotic in a case-control study of schizophrenia patients enrolled in California Medicaid. This response was not observed with 12- or 24-week exposure windows.²²⁶ A dose-response relationship for olanzapine was also reported in two studies by Gianfrancesco et al., with increases in the odds of diabetes of 22 percent ($p<0.002$) and 34 percent ($p<0.001$), respectively, noted for each 2.6 milligram increase in olanzapine dose.^{236;238} As previously noted, these results were derived by extrapolating the odds of diabetes compared to untreated patients at one month to a 12-month exposure.^{236;238} In a further study published in 2006, the same authors reported that compared to untreated patients, the odds of

developing diabetes increased with increasing olanzapine dose, which were significant for those receiving medium or high dose olanzapine.²⁴⁰

The discrepancies between the study findings may relate to differences in the study populations, the calculation and categorization of the treatment doses, and the range of doses used.

4.2.4.2.3.2 Quetiapine

Nineteen cases of diabetes (2.7%) were noted in the cohort of 700 patients treated with quetiapine included in this analysis. Using multivariate logistic regression analysis to control for differences in other variables, each one milligram increase in quetiapine dose was associated with a 0.1 percent increase in risk of diabetes, although this result was not statistically significant ($p=0.774$). Hypothesis 7c was, therefore, accepted.

Consistent with previous findings and the known epidemiology of diabetes, an increase in the odds of diabetes was noted with a comorbid diagnosis of hypertension or dyslipidemia and with increasing patient age. Increasing persistence with therapy was associated with lower odds of diabetes, while as before increased adherence was associated with higher odds of diabetes.

Information on a dose-related effect of quetiapine is sparse in the literature, with both a possible dose-related increase in risk of diabetes reported⁹ and no dose-related effect reported.²²⁶ The small number of cases in this analysis relative to the number of independent variables may have biased the findings towards the null, thereby limiting the interpretability of this result.

4.2.4.2.3.3 Risperidone

Of 4,621 patients included in this analysis, 153 (3.3%) were classified as developing new-onset diabetes. Using multivariate logistic regression analysis to control for differences in other variables, each one milligram increase in risperidone dose was associated with a three percent reduction in the risk of

diabetes, although this result was not statistically significant ($p=0.639$). Hypothesis 7d was, therefore, accepted. Trends in the odds of diabetes for all other covariates were consistent with those discussed in previous analyses.

This result supports the limited findings in the literature that the risk of diabetes does not alter according to the dose of risperidone used.^{9;226;236;238}

4.2.4.2.4 Treatment Indication

The association between treatment indication and the incidence of diabetes was examined individually for the second-generation antipsychotic agents (olanzapine, quetiapine and risperidone) using Model 3. The hypothesis testing and statistical results are summarized in Table 3.32. As noted previously, hypotheses 8a and 8e relating to clozapine and ziprasidone, respectively, were not tested due to inadequate sample sizes.

Whereas the incidence of diabetes was found to differ according to the treatment indication for patients treated with olanzapine ($p=0.034$), no association was found for patients treated with quetiapine (0.851) or risperidone ($p=0.292$). Therefore, hypothesis 8b (olanzapine) was rejected and hypotheses 8c (quetiapine) and 8d (risperidone) were accepted. For patients treated with olanzapine, the odds of new-onset diabetes were increased for all treatment indications (with the exception of dementia) when compared to a diagnosis of schizophrenia, after controlling for all other variables. Only two contrasts were significant, that is, when comparing a diagnosis of psychotic or nonpsychotic disorder to schizophrenia. Trends in the incidence of diabetes according to mental health diagnosis were not consistent between the olanzapine, quetiapine and risperidone. As noted previously, possible differences in access to care, and in particular to medical monitoring, according to the primary mental health diagnosis may have contributed to an under-detection of new-onset of diabetes among patients with schizophrenia

While schizophrenia and the affective disorders have been associated with an increased risk of diabetes independent of antipsychotic use, the literature among patients taking antipsychotics is sparse. The majority of studies have reported a non-significant association between patient mental health diagnosis and risk of diabetes. Conflicting findings have been reported from four U.S. studies using cohorts of patients enrolled in managed care organizations. Using a cohort of patients with an ICD-9 for schizophrenia, bipolar disorder or major depressive disorder, Gianfrancesco et al. noted an increase in odds of diabetes with a schizophrenia diagnosis compared to bipolar disorder (30-70%) or major depressive disorder (40-100%), after controlling for all other factors. In a study including all patients with a mental health disorder, Miller et al. noted an increase in risk of diabetes with a diagnosis of schizophrenia (HR: 1.622; 95%CI: 1.232-2.132), bipolar disorder (HR: 1.355; 95%CI: 1.073-1.711) and post-traumatic stress disorder (HR: 1.691; 95%CI: 1.019-2.806) and a decreased risk with 'other psychoses (HR: 0.602; 95%CI: 0.389-0.931). In direct contrast, Gianfrancesco et al. reported a decrease in the odds of diabetes associated with a diagnosis of schizophrenia (OR: 0.445; p=0.1076), bipolar disorder (OR: 0.444, p=0.0100) or major depression (OR: 0.449, p=0.0015) compared to patients with other psychoses. Lee et al. in a study of patients prescribed first or second-generation antipsychotics noted a similar decrease in the odds of diabetes for patients with bipolar disorder p=0.425).

4.3 Study Limitations

Several factors limit the validity of the study findings, many of which were inherent to the nature of the study, that is, a retrospective cohort study using a claims database. Although considered to be reliable and valid for the study of drug use, exposure to a drug was inferred from claims filed as opposed to having information on drug taken. It is possible that patients may have had other sources of prescription medication coverage, although, the more likely reason for not capturing data would be if patients were hospitalized or incarcerated during the follow-up period. The absence of Medicare claims data for patients that were dual-eligible for Medicaid and Medicare benefits may have led to an underreporting of both prevalent and incident cases of diabetes. This may have preferentially affected patients prescribed risperidone, the majority of whom were older and more likely to be dual-eligible for benefits. The study was strengthened, however, by the use of both medical and prescription claims to detect diabetes, reducing the risk of possible misclassification bias.

Information on several important risk factors for diabetes was missing from this database and had the potential to confound the results. These included: patient weight or body mass index; family history of diabetes; lifestyle habits; and fasting insulin and blood glucose levels. The period for this study was chosen as it predated the publication of studies regarding the association between antipsychotic use and development of diabetes, that is, to minimize channeling bias whereby patients at high risk of diabetes could be channeled away from agents perceived to have a higher risk of diabetes. It is possible that channeling still occurred, in that physicians may have channeled overweight or obese patients, or those perceived to be at higher risk of diabetes, away from clozapine and olanzapine, because of concerns about the greater potential for weight gain with these agents. This may have spuriously lowered the association between use

of clozapine or olanzapine and risk of diabetes and increased the apparent risk of diabetes with a more weight-neutral agent such as risperidone.

The primary dependent variable in this study was the occurrence of new-onset diabetes which was measured by the detection of an ICD-9 code for diabetes, or the prescription of insulin, an oral hypoglycemic agent, or an insulin sensitizing agent. As previously noted, the prescription medications used to treat diabetes are disease-specific for diabetes, with limited off-label use for other indications. This study was strengthened by the consideration of both medical and pharmacy claims for diabetes, reducing the likelihood that either prevalent or incident cases were misclassified. Because of possible left-censoring of the data, it is not certain, however, that all of the first-listed claims for diabetes represent new-onset of illness. This concern is mitigated by the use of a 6-month window prior to the index data. Similarly, it is possible that patients with latent diabetes were included among the incident cases because of the clinical nature of this disease, that is, a prolonged asymptomatic course with detection based on contact with a physician and testing. It is unlikely however, that this would distribute differently between the index agents. Possible differences in the access to care for patients with serious mental illness, and also the availability of medical monitoring in ambulatory mental health settings may have reduced the apparent risk of prevalent or new-onset diabetes in the cohort, confounding the study findings. In particular, diabetes may have been under detected in patients with schizophrenia, possibility distorting the studies findings with regard to the association between risk of diabetes and the primary mental health diagnosis.

A limitation of the study is that the ICD-9 codes were not independently validated, resulting in possible misclassification of the mental health diagnoses and of cases of diabetes. The ICD-9 coding system has been widely used in claims based research, and although the true number of affected patients may be

over or underestimated, this system has been shown to be accurate for schizophrenia patients enrolled in Medicaid.³⁵⁸ While acknowledging that misclassification of diagnoses may have occurred, it is unlikely that these were unevenly distributed between the index agents. It is possible that the hierarchical approach used to classify patients according to their primary mental health diagnosis may have led to a number of patients being misclassified. The approach was nevertheless supported by the consistency in treatment-related antipsychotic dosing patterns between this and other studies.

As this study was limited to those patients that were prescribed antipsychotic monotherapy and may, therefore, not be generalizable to the use of antipsychotic polypharmacy. Anecdotal reports suggest that the prevalence of antipsychotic polypharmacy may have been lower during the time-frame of this study (1997-2001), but that it has increased in recent years. It is also possible that the use of polypharmacy is lower in Texas Medicaid than elsewhere because of the restriction of program recipients to a maximum of three prescriptions per month. While antipsychotic polypharmacy was not explicitly examined in this study, 1,300 patients, (6.7%) had a switch to polypharmacy as their study endpoint. The risk of new-onset diabetes associated with use of combination antipsychotic therapy may need to be addressed in the future, particularly given reports of the increasing prevalence of polypharmacy with these agents.

The large sample size strengthened the study providing adequate power for the majority of the statistical analyses. However, the study may not have been adequately powered to detect the impact of treatment dose given the small number of cases of diabetes among those categorized as receiving 'high dose' therapy and among quetiapine recipients. The risk of type I errors may have been further increased by the large number of pair-wise comparisons in the regression analyses.

The study population may not be generalizable to the U.S. population prescribed antipsychotic therapy. The cohort was a heterogeneous group with a diverse range of treatment conditions and was comprised of mainly older adults, with an over-representation of women and minorities. While the prescribing of antipsychotics varied according to demographic and clinical variables, these variables were included as covariates in the regression analyses and accordingly were not expected to bias the study findings. Those with a lower socio-economic status are over-represented in Medicaid compared to the national population; however, this is less of a concern in a study of patients with serious mental illness, the majority of whom receive publicly funded healthcare.³⁶⁵

4.4 Practical Significance and Future Research

In spite of the limitations reported herein, the pattern of results observed is consistent with those of previously published studies. That is, after controlling for other risk factors, the second-generation antipsychotics do not differ significantly in their potential to cause new-onset diabetes. This consistency across studies that differed in study design, study population and analysis plan, increases the credibility of the findings. Discrepancies between the findings of this and other studies may possibly be explained by differences in the population studied, differences in the definition of diabetes and antipsychotic exposure used, the number and type of covariates included, and statistical analysis plans.

What deserves elaboration is the magnitude of the association reported in the different studies. When compared to a first-generation antipsychotic, the relative risk of diabetes associated with the second-generation antipsychotics has ranged from 1.1 to 2.6 in the published literature, with the majority reporting a relative risk of 1.6 or less. It is important to assess this risk in terms of the absolute rather than the relative risk of diabetes. In 2004, the annual incidence of diabetes among adults between 18 and 79 years of age was 0.7 percent (1 in 1,429).²⁷⁶ Using a conservative estimate that the incidence of diabetes does not differ for those with a mental health diagnosis compared to the general U.S. population, an odds ratio of 1.6 would increase the absolute risk of diabetes to 1.12 percent (1 in 892). Under the more conservative assumption that patients with mental health diagnoses have an incidence of diabetes that is twice that of the general U.S. population (1.4%), exposure to a second-generation instead of a first-generation antipsychotic would increase that risk to 2.24 percent (1 in 446). Similarly, using the annual incidence of diabetes established in this study population of 2.37 percent (1 in 422), exposure to a second-generation versus a

first-generation agent would increase the absolute risk to 3.79 percent (1 in 264) cases per year.

While not diminishing the importance of such an increase in risk of diabetes with the second-generation antipsychotics, the clinical implication of such an increase must be considered in the context of the available options. For a patient with treatment-refractory schizophrenia, the additional risk of diabetes that may present with use of clozapine is likely to be off-set by the benefit of treatment. Among non-refractory patients, while there is little to discriminate between the other second-generation agents, although olanzapine was found to have a modest increase in efficacy in the CATIE trial. Allowing that patients treated with olanzapine were also more likely to discontinue treatment because of metabolic effects, the possible increase in effectiveness would need to be considered in the context of other risk factors that the patient may have for diabetes.²⁵⁴ It is worth reiterating that the increase in mean exposure-adjusted blood glucose levels for olanzapine and risperidone were 13.7 ± 2.5 milligrams per deciliter (mg/dL) and 6.6 ± 2.5 mg/dL, respectively, representing a net mean difference of only 7.1 mg/dL.²⁵⁴ This could be sufficient to precipitate diabetes in a patient with baseline glucose intolerance; however, such an increase in blood glucose levels could be easily managed with either lifestyle intervention or minimal pharmacological therapy. The efficacy of education and lifestyle-intervention to delay the onset, or decrease the incidence of diabetes in a non-psychotic population has been well documented.^{388;389} When considered in the context of a high-risk cohort such as patients with schizophrenia or bipolar disorder, such intervention could be of even greater benefit, acknowledging of course the difficulties of implementing such programs in patients with serious mental illness.

Suggestions for future research include further prospective trials to assess the metabolic effects of antipsychotic treatment in conditions other than schizophrenia, such as bipolar disorder and dementia. The risk of new-onset diabetes associated with use of antipsychotic polypharmacy should also be considered, particularly given the reports of the increasing prevalence of antipsychotic polypharmacy prescribing. The efficacy of intensive lifestyle education programs in patients with serious mental illness to delay or prevent complications of diabetes would also be of interest.

4.5 Conclusions

Among patients enrolled in Texas Medicaid taking antipsychotic therapy, the risk of new-onset diabetes did not vary based on exposure to a first-generation antipsychotic, olanzapine, quetiapine or risperidone; a finding that persisted after controlling for demographic, clinical and other medication-related variables. Consistent with other studies and national trends, increasing age, Hispanic and African American race or ethnicity, comorbid hypertension and dyslipidemia were significant independent risk factors for the development of diabetes. With the exception of a possible association between mental health diagnosis and diabetes in patients treated with olanzapine, neither antipsychotic dose nor treatment indication was associated with the risk of new-onset diabetes.

This study contributes to the body of literature on the comparative safety of the second-generation antipsychotic agents. It expands on the previous literature in that it considered a heterogeneous patient population prescribed antipsychotics – in line with the diverse range of patients that are treated with these agents in clinical practice. Given the baseline risk of cardiovascular and metabolic disorders in the elderly, and among patients with schizophrenia and bipolar disorder, the risks associated with use of the second-generation antipsychotics must be considered in the context of the clinical benefits and the financial setting. All patients should be assessed at baseline for diabetes and monitored routinely in accordance with recent guidelines, with appropriate allocation of funding to enable providers provide such services in ambulatory mental health clinics.

Use of the second-generation antipsychotic must also be placed in context of the rapid and occasionally fatal acute metabolic decompensation (including ketoacidosis) that has been reported with these agents. Although rare, these events have been reported with all of the second-generation agents, albeit more

frequently with olanzapine and clozapine. While insufficient to avoid use of these agents, healthcare providers and patients must be alert to this potential so that patients can be rapidly identified and treated.

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
1 ¹⁴⁵	AA, M, 41	Clozapine 900mg	Benzotropine	Schizophrenia	N/NR	8	New onset diabetes	NR	829	NR	Resolved on DC of SGA
2 ¹⁴⁶	AA, F, 34	Clozapine 250mg	Lithium Benzotropine	Schizophrenia	N/Y	6	DKA	NR	1224	NR	Resolved on DC of SGA
3 ¹⁴⁷	NR, M, 42, Obese - 130Kg	Clozapine 350mg	NR	Psychotic disorder	N/Y	4	DKA	NR	447	NR	Ongoing IGT despite DC SGA
4 ¹⁴⁸	AA, M, 46	Clozapine 500mg	Lithium	Schizophrenia	N/Y	5	DKA	NR	762	NR	Continued DM (insulin) despite DC SGA
5 ¹⁴⁹	AA, M, 32, 11%>IBW	Clozapine 425mg	Propranolol	Schizophrenia	N/Y	8	DKA	NR	930	+3.6	Resolved on DC SGA, however hyperglycemia on re-challenge
6 ¹⁴⁹	AA, M, 44, 42%>IBW	Clozapine 450mg	Risperidone ¹ HCTZ Lithium	SAD	N/N	5	New onset diabetes	8.7	494	+1.4	Clozapine & OHA
7 ¹⁴⁹	C, M, 51	Clozapine 200mg	Glyburide	Schizophrenia	Y/NR	5	Decreased glycemic control	NR	500	0	Clozapine & insulin
8 ¹⁴⁹	AA, M, 51	Clozapine 900mg	Glyburide Lisinopril	Schizophrenia	Y/NR	2	Decreased glycemic control	NR	311	NR	Risperidone, chlorpromazine & OHA
9 ¹⁴⁹	NR, M, 50	Clozapine 300mg	NR	Schizophrenia	N/NR	1.4	DKA	NR	423	NR	Continued DM (insulin) despite DC SGA

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
10 ¹⁵⁰	C, M, 37	Clozapine Dose NR	NR	Schizophrenia	N/NR	11	New onset diabetes, Lactic acidosis	NR	1000	NR	Fatal MI ²
11 ¹⁵¹	Black ³ , M,30	Clozapine 300mg	Minocycline	Schizophrenia	N/N	20	DKA	NR	448	NR	Olanzapine & OHA
12 ¹⁵²	C, M, 48	Clozapine 150mg	Lithium Niaicin	Schizophrenia	N/NR	2.6	New onset diabetes	NR	267	NR	Resolved on switching to risperidone
13 ¹⁵³	AA, M, 47, 20% >IBW	Clozapine 150mg	NR	Schizophrenia	N/N	8	New onset diabetes	NR	NR	+10.9	Ongoing DM (OHA) despite DC SGA
14 ¹⁵³	AA, M, 32 Overweight	Clozapine 400mg	NR	SAD	N/N	72	DKA	NR	NR	+25.5	Clozapine & OHA
15 ¹⁵³	AA, M, 43 20% >IBW	Clozapine 100mg	NR	Schizophrenia	N/Y	NR	New onset diabetes	NR	NR	BMI ↑ 8%	Clozapine & OHA
16 ¹⁵³	AA, M, 41 38% > IBW	Clozapine 200mg	NR	NR	N/N	5	New onset diabetes	NR	1028	NR	Risperidone & OHA
17 ¹⁵³	AA, M, 38 50% > IBW	Olanzapine 25mg	NR	Schizophrenia	N/Y	12	New onset diabetes	NR	NR	+5	Olanzapine & OHA
18 ¹⁵³	C, M, 56 25% > IBW	Olanzapine 25mg	NR	Schizophrenia	N/N	12	New onset diabetes	NR	NR	0	Olanzapine & OHA
19 ¹⁵⁴	AA, M, 32 BMI = 34.4	Olanzapine 20mg	Benzotropine	Psychotic disorder / personality disorder	N/N	6	New onset diabetes	13.8	402	NR	Resolved on switch to FGA, recurrence of hyperglycemia on re-challenge

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
20 ¹⁵⁵	C, M, 31 BMI = 29	Clozapine 200mg	NR	SAD	N/N	12	DKA	NR	756	+3.2	Resolved on DC; Recurred on re-challenge
21 ¹⁵⁶	Black ⁴ , M, 40 Mild obesity	Clozapine Dose NR	NR	Schizophrenia	N/N	2.3	DKA	NR	990	NR	Clozapine & insulin
22 ¹⁵⁷	AA, M, 30	Clozapine 325mg	NR	Schizophrenia	N/N	12	DKA	NR	342	NR	FGA & OHA
23 ¹⁵⁸	C, F, 50	Clozapine 400mg	Valproic Acid	Bipolar disorder	N/Y	4	DKA	NR	1000	NR	Resolved (ongoing IGT) on reduced dose (100mg)
24 ¹⁵⁹	C, M, 31 BMI = 40	Olanzapine 10mg	NR	Schizophrenia	N/N	12	DKA	14.7	648	-4.1	Resolved on DC
25 ¹⁶⁰	AA, M, 50 Mild obesity	Olanzapine 30mg	Fluphenazine Divalproex Benztropine	Schizophrenia	N/N	32	DKA	NR	1200	+9.5	Resolved on DC
26 ¹⁶¹	C, F, 42 BMI = 36	Olanzapine 10mg	NR	SAD	N/Y	24	DKA	NR	1274	+32.3	Quetiapine & insulin
27 ¹⁶¹	C, F, 40 BMI = 27.2	Olanzapine 10mg	NR	Schizophrenia	N/N	68	DKA	NR	1160	+4.5-6.8	Resolved on DC
28 ¹⁶¹	C, F, 40 Obese	Olanzapine 10mg	Valproic acid MPA	Bipolar disorder	N/N	20	New onset diabetes	NR	766	NR	Resolved on DC

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
29 ¹⁶¹	C, M, 47 BMI = 40	Olanzapine 10mg	CBZ	SAD	N/Y	5	New onset diabetes	NR	878	+13.6	Resolved on DC but recurred on re-challenge and persisted despite switch to quetiapine (insulin)
30 ¹⁶¹	C, M, 43 Obese	Olanzapine 10mg	Lithium Lamotrigine Paroxetine	Bipolar disorder	N/N	2	New onset diabetes	10.4	567	+25	Quetiapine & OHA
31 ¹⁶¹	C, M, 39, BMI = 39.1	Olanzapine 5-10mg	Lithium Valproic acid HCTZ Lisinopril	SAD	N/Y	14	New onset diabetes	NR	686	-2.7	Risperidone & OHA
32 ¹⁶¹	C, M, 38 BMI = 31.3	Olanzapine 5-10mg	Sertraline	Schizophrenia / OCD	N/N	12	New onset diabetes	NR	372	0	Resolved on DC (diet control)
33 ¹⁶²	AA, M, 45	Olanzapine 10mg	Glyburide	MDD	Y/N	4	Decreased glycemic control	NR	500	↑ 25%	Resolved on DC
34 ¹⁶³	C, M, 42	Quetiapine 200mg	Lithium Venlafaxine	Bipolar disorder	N/N	4	New onset diabetes	NR	607	NR	Resolved on DC
35 ¹⁶⁴	Black ³ , M, 19 60Kg	Olanzapine 20mg	NR	Schizophrenia	N/N	4	DKA	18.6	876	-3	Risperidone & insulin
36 ¹⁶⁵	NR, M, 45 BMI = 35.2	Clozapine 900mg		Schizophrenia	N/N	68 - 156 ⁴	New onset diabetes	NR	324	+ 23.2 (6 yrs)	Clozapine & OHA

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
37 ¹⁶⁵	NR, M, 45 BMI = 36.1	Clozapine 800mg	Metoprolol Lisinopril	Schizophrenia	N/N	12- 260 ⁵	New onset diabetes	NR	327	+19.5 (7 yrs)	Clozapine & OHA
38 ¹⁶⁶	NR, M, 38 BMI = 27	Clozapine (Dose NR)	NR	Schizophrenia	N/N	24	DKA	10.7	450	-3.2	Resolved on DC
39 ¹⁶⁶	NR, M, 55, BMI = 28	Olanzapine 20mg	NR	Recurring depression	N/Y	16	New onset diabetes	16.7	342	-7.0	Resolved on DC
40 ¹⁶⁷	AA, F, 54 BMI = 25	Olanzapine 10mg	Fluoxetine	MDD with psychoses	Y/NR	1.7	Decreased glycemic control	6.5	536	+ 13.2	Poor control despite switch to quetiapine, improved on DC
41 ¹⁶⁸	C, M, 42	Risperidone 4mg	Fluoxetine Trazadone	MDD with psychoses	N/N	28	DKA	11.4	565	NR	Quetiapine & insulin
42 ¹⁶⁹	AA, M, 30 BMI = 32.3	Quetiapine 300mg	Divalproex Loxapine Fuphenazine	SAD	N/N	16.5	New onset diabetes	13.3	382	+5.0	Resolved on DC
43 ¹⁷⁰	AA, M, 38, BMI = 30.7	Clozapine 300mg	Sertraline	SAD	N/N	9.5	New onset diabetes	NR	1000	NR	Resolved on DC
44 ¹⁷¹	AA, F, 34 72.3Kg	Olanzapine 20mg	NR	Schizophrenia	NR	10	New onset diabetes	NR	404	+7.7	Olanzapine & insulin
45 ¹⁷¹	AA, F, 20 75.5Kg	Olanzapine 20mg	Valproate	SAD	NR/Y	4	New onset diabetes	NR	249	+3.6	Resolved on DC
46 ¹⁷¹	AA, M, 54 84.1Kg	Olanzapine 20mg	NR	NR	NR	4	New onset diabetes	NR	405	+9.5	Olanzapine, OHA & insulin
47 ¹⁷¹	AA, M, 42 84.1Kg	Olanzapine 20mg	Valproate	Schizophrenia	NR/Y	18	Diabetic coma	NR	800	+9.5	Olanzapine & insulin

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
48 ¹⁷¹	C, M, 38 80Kg	Olanzapine 5mg	NR	Schizophrenia	NR/Y	12	New onset diabetes	NR	395	+2.7	Ongoing DM (insulin) despite DC
49 ¹⁷¹	AA, M 53	Olanzapine 20mg	NR	Schizophrenia	NR/Y	24	New onset diabetes	NR	220	+23.6	Olanzapine & OHA & insulin
50 ¹⁷¹	AA, F, 35	Olanzapine 10-20mg	Valproate	Schizophrenia	NR/Y	20	New onset diabetes	NR	374	NR	Olanzapine, OHA & insulin
51 ¹⁷¹	C, M, 49 112.3Kg	Olanzapine 10mg	NR	Schizophrenia	NR	4	New onset diabetes	NR	125	+11.8	Olanzapine & OHA
52 ¹⁷²	C, M, 33 BMI = 32.5	Clozapine 100mg	Sertraline Trihexphenidyl	Schizophrenia	N/N	32	DKA	14	626	-20.9	Resolved on DC
53 ¹⁷³	AA, F, 46 BMI = 39	Olanzapine 15mg	Valproic acid CBZ	Bipolar Disorder	N/Y	60	DKA Pancreatitis	11.7	957	+2.7	Risperidone, OHA & insulin
54 ¹⁷⁴	C, M, NR 97.3Kg	Olanzapine 20mg	Quetiapine 25mg ⁶ Valproic acid	SAD	N/N	156	New onset diabetes	11	417	+1.8	DM resolved on switching to risperidone ³
55 ¹⁷⁵	AA, M, 52 BMI = 30.1	Risperidone 8mg	NR	Schizophrenia	N/Y	64	New onset diabetes	NR	436	- 0.9	Risperidone & insulin
56 ¹⁷⁵	HIS, M, 50 BMI = 26.9	Risperidone 6mg	NR	Schizophrenia	NR/NR	132	New onset diabetes	NR	158	+ 29.5	Risperidone & OHA
57 ¹⁷⁶	C, M, 57 71.6Kg	Olanzapine 5mg	Paroxetine	Schizophrenia	N/Y	24	New onset diabetes	NR	153	+15.9	Resolved on switch to quetiapine
58 ¹⁷⁶	AA, M, 48	Clozapine 600mg	Lithium Citalopram	SAD	N/Y	52	New onset diabetes	6.1	246	-7.3 (1 yr)	Clozapine & insulin

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
59 ¹⁷⁶	C, F, 36 Obese 112Kg	Risperidone 4mg	NR	Depression NOS	N/Y	8	New onset diabetes	NR	182	+ 4.5	Risperidone & diet control
60 ¹⁷⁶	C, M, 41	Risperidone 12mg	Propranolol Fluoxetine	Schizophrenia	N/Y	64	New onset diabetes	NR	271	NR	Risperidone & diet control
61 ¹⁷⁷	C, M, 43 BMI = 29	Clozapine 400mg	NR	Schizophrenia	NR/NR	208	New onset diabetes	NR	181	+ 18.2	Olanzapine & OHA
62 ¹⁷⁷	C, M, 28 BMI = 23.4	Clozapine 350mg	NR	Schizophrenia	NR/NR	104	New onset diabetes	NR	407	+ 13.6	Olanzapine & OHA
63 ¹⁷⁸	C, M, 38 BMI = 27	Olanzapine 20 mg	Valproic acid Venlafaxine Propranolol	Schizophrenia	N/Y	36	DKA	13.4	765	+13.6	Olanzapine & insulin
64 ¹⁸⁰	C, M, 51 7% > IBW	Olanzapine 25mg	NR	PTSD & Bipolar disorder	N/N	< 24	Hyperosmolar, hyperglycemic nonketonic coma	13.3	1596	0	Resolved on DC
65 ¹⁷⁹	AA, M, 31 BMI = 28.4	Olanzapine 15mg	Divalproex Mirtazapine	SAD	N/Y	6	New onset diabetes	10.7	509	+11.8	Perphenazine & insulin; decreased control on switch to olanzapine
66 ¹⁷⁹	C, M, 44 BMI = 26	Olanzapine 10mg	Divalproex Sertraline Propranolol	SAD	N/Y	16	New onset diabetes	NR	936	NR	Olanzapine & OHA

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
67 ¹⁸¹	C, F, 79 BMI = 20.8	Olanzapine 2.5mg	Mirtazapine Clonednole	Depressive disorder	IGT/NR	6	New onset diabetes	NR	496	NR	Resolved on DC
68 ¹⁸²	C, M, 45 Obese 114.5Kg	Olanzapine 20-25mg	Atenolol Lisinopril Nefazadone	Schizophrenia	N/N	72	New onset diabetes	13.5	NR	+ 6.4	Risperidone & OHA
69 ¹⁸³	AA, M, 27 BMI = 27 ⁷	Olanzapine 10mg	Valproic acid	Schizophrenia	N/N	124	DKA	NR	1240	NR	Olanzapine & OHA
70 ¹⁸⁴	C, F, 64 BMI = 31	Olanzapine 10mg	Valproic acid Lithium	Bipolar disorder	Y/NR	18	Decreased glycemic control	NR	1240	+8.9	Ongoing DM (insulin) despite DC but with improved glycemic control
71 ¹⁸⁵	NR, F, 19 BMI = 25.3	Olanzapine 20mg	Metoprolol	Psychotic disorder	N/NR	12	New onset diabetes	NR	338	NR	Resolved on DC
72 ¹⁸⁵	NR, M, 24 BMI = 22.3	Olanzapine 20mg	NR	Psychotic disorder	N/NR	0.7	DKA with cardiovascular collapse	NR	>500	NR	Died
73 ¹⁸⁶	C, M, 49 BMI = 34.2	Olanzapine 20mg	NR	Schizophrenia	N/NR	50	DKA	6.5	766	+15.5	Resolved despite ongoing olanzapine
74 ¹⁸⁷	NR, M, 42 BMI = 28	Olanzapine 20mg	NR	Schizophrenia	N/NR	NR	New onset diabetes	NR	266	+6.8	Resolved on switch to ziprasidone

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
75 ¹⁸⁸	NR, F, Middle-aged	Ziprasidone 40mg ⁸	Clozapine Lithium	SAD	N/NR	2	New onset diabetes, Pancreatitis and Rhabdomyolysis	NR	980	NR	Resolved on DC ziprasidone despite resuming clozapine
76 ¹⁸⁹	C, M, 44 Obese, 144.5Kg	Olanzapine 15mg	Haloperidol Divalproex	SAD	N/N	2.6	New onset diabetes	18.2	603	NR	Thioridazine & OHA
77 ¹⁹⁰	C, F, 51 BMI = 26.7	Olanzapine 30mg	Metformin Gliclazide	SAD	Y/NR	3	Decreased glycemic control	NR	360	0	Control regained on switch to FGA
78 ¹⁹¹	Black ³ , M, 33 60.7Kg	Olanzapine 30mg	None	Schizophrenia	N/NR	12	DKA	NR	675	+8.6	Resolved on DC hyperglycemia on re-challenge with olanzapine and on exposure to clozapine
79 ¹⁹²	NR, M, 31 BMI = 29	Olanzapine 20mg	NR	Schizophrenia	N/N	4	Hyperosmolar, nonketonic diabetic coma	NR	954	+0.9	Death
80 ¹⁹³	C F, 39 BMI = 24	Risperidone 8mg	Stavudine Didanosine Nevirapine Haloperidol Paroxetine	Schizophrenia	N/N	156	New onset diabetes	NR	328	0	Resolved on DC

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
81 ¹⁹⁴	AA, F, 44 61.8Kg	Olanzapine 25mg	Haloperidol Phenytoin	Schizophrenia	N/N	4	DKA	NR	>500	+3.6	Resolved on DC; no reemergence with ziprasidone
82 ¹⁹⁵	NR, M, 49 BMI = 26.4	Olanzapine 20mg	NR	Schizophrenia	N/N	20	New onset diabetes	NR	275	+10	Resolved on DC
83 ¹⁹⁶	C, F, 18 65Kg	Olanzapine 10mg	NR	Schizophrenia	N/Y	20	New onset diabetes	11.5	268	+21.4	Resolved on DC
84 ¹⁹⁷	Asian, M, 28 BMI = 26.2	Olanzapine 10mg	NR	Schizophrenia	NR/Y	4	DKA	13.7	1080	-9.1	Resolved on DC
85 ¹⁹⁸	Black ³ , F, 45 Obese	Quetiapine ⁹ Dose NR	Risperidone Dose NR	Bipolar disorder	N/NR	“soon after”	New onset diabetes	NR	600	0	Resolved on DC of quetiapine, no recurrence on switch to ziprasidone
86 ¹⁹⁹	Asian, M, 49 BMI = 27.6	Olanzapine 20 mg	Haloperidol Fluphenazine Levo-promepazine	NR	N/Y	45	New onset diabetes	NR	169	BMI ↓1.5	Continued DM (OHA) despite DC
87 ¹⁹⁹	Asian, M, 45 BMI = 27.2	Olanzapine 40 mg	Levo-promepazine	NR	N/N	48	New onset diabetes	NR	160	BMI ↓4.9	No resolution on DC
88 ¹⁹⁹	Asian, F, 25	Olanzapine 15 mg		NR	N/N	47	Transient hyperglycemia	NR	220	NR	Resolved without DC
89 ¹⁹⁹	Asian, M, 28 BMI = 22.1	Olanzapine 20 mg	Zotepine Fluphenazine	NR	N/N	47	Transient hyperglycemia	NR	215	BMI ↑1.5	Resolved without DC

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
90 ¹⁹⁹	Asian, M, 55 BMI = 23.6	Olanzapine 25 mg	Levo-promepazine	NR	N/N	50	Transient hyperglycemia	NR	212	BMI ↑2.4	Resolved without DC
91 ²⁰⁰	NR, F, 51	Clozapine 400mg	HTCZ	Schizophrenia	IGT/NR	1.4	New onset diabetes	NR	476	3.0	Pimozide & OHA
92 ²⁰⁰	NR, M, 35, Overweight 88Kg	Olanzapine 15mg		Schizophrenia	N/NR	11	New onset diabetes	NR	151	0	Resolved without DC (diet)
93 ²⁰⁰	C, M, 35	Olanzapine 10mg		Schizophrenia	IGT/NR	9	New onset diabetes	NR	342	+8.0	Olanzapine & OHA
94 ²⁰⁰	NR, F, 36, Metabolic syndrome	Olanzapine 20mg		Schizophrenia	N/NR	32	New onset diabetes	NR	264	+10.0	Risperidone & OHA
95 ²⁰⁰	NR, M, 48, BMI = 29.7 ⁷	Olanzapine 20mg	Lithium Clomipramine	SAD	N/Y	182	Hyperosmolar nonketonic coma	NR	1972	Yes	Risperidone & insulin; Organic brain disorder post coma
96 ²⁰⁰	NR, F, 65	Clozapine 75mg	Fluphenazine	Schizophrenia	Y/NR	4	Decreased glycemic control	NR	445	NR	Clozapine & OHA
97 ²⁰⁰	NR, M, 69	Olanzapine 10mg	Oxazepam Losarten	Recurrent depressive disorder with psychoses	Y/NR	0.6	Decreased glycemic control	NR	252	4	Resolved on DC
98 ²⁰⁰	NR, M, 51	Olanzapine 5 mg	Sertraline Mirtazapine Insulin	Recurrent depressive disorder	Y/NR	6	Decreased glycemic control	NR	230	NR	Resolved on DC

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

Case	Race, Gender, Age, BMI/Weight	Medication (daily dose)	Concomitant Medications	Diagnosis	Hx DM (Patient /Family)	Time to Onset (wks)	Event	HbA _{1c} (%)	Max Blood Glucose mg/dL	Weight Change (Kg)	Resolution / Re-challenge
99 ²⁰⁰	NR, F, 38 BMI = 28.5	Olanzapine 20mg		Schizophrenia	Y/NR	3.5	Decreased glycemic control	NR	411	8	Sertindole & insulin

Abbreviations		
<i>AA</i> – African-American	<i>HCTZ</i> – Hydrochlorothiazide	<i>OCD</i> – Obsessive Compulsive Disorder
<i>BMI</i> – Body Mass Index (Kg/m ²)	<i>IBW</i> – Ideal Body Weight	<i>OHA</i> – Oral Hypoglycemic Agent
<i>C</i> – Caucasian	<i>M</i> – Male	<i>SAD</i> – Schizoaffective Disorder
<i>CBZ</i> - Carbamazepine	<i>MDD</i> - Major Depressive Disorder	<i>SGA</i> – Second-Generation Antipsychotic
<i>DC</i> – Discontinued	<i>MI</i> – Myocardial Infarction	<i>Wks.</i> – Weeks
<i>DKA</i> - Diabetic Ketoacidosis	<i>MPA</i> – Medroxyprogesterone	<i>Y</i> – Yes
<i>DM</i> – Diabetes Mellitus	<i>Mo.</i> – Month	<i>Yr</i> – Year
<i>F</i> – Female	<i>N</i> – No	
<i>FGA</i> – First Generation Antipsychotic	<i>NR</i> – Not Reported	

Appendix A: Summary of Case Reports of New-Onset Diabetes, Hyperglycemia, or Diabetic Ketoacidosis Associated with Second-Generation Antipsychotic Therapy in Adults (continued)

1. Clozapine added to a stable regimen of risperidone 6mg daily with new emergence of diabetes mellitus with poor glycemic control.
2. Clozapine discontinued four days prior to the myocardial infarction.
3. 'Black' race includes: Afro-Caribbean, African and Aboriginal races.
4. Patient developed diabetes between 68 and 156 weeks after commencing clozapine therapy.
5. Patient developed diabetes between 12 and 260 weeks after commencing clozapine therapy.
6. Hyperglycemia first documented 6 days after adding quetiapine to a stable regimen of olanzapine 20mg daily. Patient was stabilized, with reducing doses of insulin after discontinuation of olanzapine (patient maintained on quetiapine and haloperidol). Re-emergence of poor glycemic control on switching therapy back to olanzapine. Patient switched to risperidone with subsequent resolution of diabetes.
7. Not a baseline value.
8. Patient stabilized and asymptomatic for years on clozapine and risperidone.. Two weeks after switching risperidone to ziprasidone patient developed rhabdomyolysis, pancreatitis and hyperglycemia. Clozapine and ziprasidone discontinued; however clozapine subsequently successfully restarted without re-emergence of symptoms.
9. Hyperglycemia resolved on discontinuation of quetiapine with no re-emergence when ziprasidone started. Risperidone use preceded quetiapine and was co-prescribed throughout.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Barner ²²⁸ 2003	Cohort	Central Texas Veterans Affairs database	09/95-11/02	Any patient \geq 18 years treated with an FGA or SGA with continuous enrollment for 12 mo. Exclude if: use of an AP in 6 mo. pre-enrollment; or DM in 12 mo. pre-enrollment.	New-onset DM defined as: new Rx for OHA /insulin; an ICD-9 of 250.xx; or blood glucose \geq 200mg/dL.	Multiple logistic regression	Age, gender, race, persistence, mental health, BMI, hypertension, hyperlipidemia.
Buse ⁹ 2003	Cohort	Advance PCS prescription claims database	12/98-08/00	Any patient \geq 18 years treated with AP monotherapy compared to general population not on AP (no AP in 6 mo. pre- or post-enrollment). Exclude if: use of an AP in 6 mo. pre-enrollment; or DM in 12 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA /insulin.	Cox proportional hazard function	Mean age, gender, mean dose of AP, duration of Tx.
Carlson ²²⁹ 2005	Cohort	UK General Practice Research database	01/94-12/01	Any patient \geq 18 years treated with AP monotherapy. Exclude if: Hx of DM prior to enrollment; or $<$ 2yrs. continuous enrollment prior to index date for inclusion in FGA cohort.	New-onset DM defined as: a new Rx for OHA / insulin; or medical claim for T1DM or T2DM.	Cox proportional hazard function	Age, gender, obesity, duration of Tx, use of concurrent diabetogenic medication.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Caro ²³⁰ 2002	Cohort	Régie de l'Assurance Maladie du Quebec database	01/97-12/99	Any patient treated with olanzapine or risperidone. Exclude if: Rx for clozapine during study period; or if DM in 12 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA / insulin; or ICD-9 of 250.xx.	Cox proportional hazard function	Age, gender, diagnosis of schizophrenia, duration of Tx, haloperidol Rx, Rx for other AP.
Cavazzoni ²⁵¹ 2005	Post-hoc analysis of RCT	Olanzapine Clinical Trials Database	N/R	Patients with schizophrenia aged 18-65 years. Exclude if: DM at baseline (clinical diagnosis or Rx. for DM); or two glucose levels ≥ 200 mg/dL at baseline; or only baseline glucose values.	New-onset DM defined as: clinical diagnosis for DM; Rx for OHA / insulin; 2x casual blood glucose ≥ 200 mg/dL; or final random glucose ≥ 200 mg/dL.	Cox proportional hazard function	Baseline casual glucose level, baseline risk factors for DM, Tx.-emergent weight gain, study protocol. (Risk factors for DM included: Age ≥ 45 ; BMI ≥ 27 ; non-White ethnicity; HTN; baseline casual glucose level).
Citrome ²²⁵ 2004	Case-Control	New York State Psychiatric Inpatients	01/00-12/02	Hospitalized for at least 60 days. Exclude if: Rx for DM prior to index date. Controls: Matched to control group on calendar year, length of stay, race, age group and diagnosis.	Cases defined as: new Rx for DM ≥ 60 days after admission.	Cox proportional hazard function	Age, gender.
Cunningham ²³¹ 2003	Cohort	Illinois Veterans Affairs database	01/99-12/01	Schizophrenia patients (minimum 2 separate diagnoses) treated with AP monotherapy. Exclude if: prior Hx of DM; or use of AP in 3 mo. pre-enrollment.	New-onset DM defined as: 2 diagnostic codes for DM in medical record.	Cox proportional hazard function	Age, gender, race, marital status, concomitant diabetogenic drugs, measures of DM screening.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Etminan ²³² 2003	Cohort	Ontario Drug Benefit Prescription Program	N/R	Long term care residents aged ≥ 65 years treated with FGA or SGA, with ≥ 2 consecutive Rx fills (within 120% of days supply). Exclude if: DM in 12 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA /insulin.	Cox proportional hazard function	Age, gender, total number of drugs (comorbidity), SES, concomitant diabetogenic drugs.
Farwell ²³³ 2004	Cohort	Regenstried Medical Record System (claim database for inpt and ambulatory care clinics in Indianapolis)	01/72-12/00	Patients aged ≥ 18 years prescribed olanzapine, risperidone or a FGA (phenothiazine only) for ≥ 1 year. Exclude if: Rx for haloperidol or antiemetic phenothiazine; Hx. of DM (any diagnosis; DM Rx; > 1 blood glucose level $>200\text{mg/dL}$; or any HbA1c $> 9\%$).	New-onset DM defined as: a new diagnosis of DM; Rx for DM; > 1 blood glucose level $>200\text{mg/dL}$; or any HbA1c $> 9\%$ in first year of AP Tx.	Cox proportional hazard function	Age, race, gender, obesity, mental health diagnosis, alcohol/drug use, number of visits to primary care, psychiatric clinic or emergency room, pre-Tx weight, weight gain.
Feldman ²³⁴ 2004	Cohort	Advance PCS Rx claim database for managed care health plan	12/98-08/00	Patients aged ≥ 60 years prescribed AP monotherapy, enrolled for $\geq 12\text{mo.}$ index date and $\geq 6\text{mo.}$ post index date. Exclude if: DM Rx. in 12 mo. or AP Rx. in 6mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA /insulin.	Cox proportional hazard function	Age, treatment duration.
Fuller ²³⁵ 2003	Cohort	Ohio Veterans Affairs database	01/97-12/00	Any patient receiving ≥ 30 days supply of olanzapine, risperidone, fluphenazine or haloperidol. Exclude if: female; race other than AA or Caucasian; use of clozapine or Hx of DM in 12 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA /insulin; or an OPD ICD-9 250.xx.	Cox proportional hazard function	Race, age, ICD-9 of 290.xx (individual covariates), number of days supplied, previous or concurrent Rx for valproic acid, lithium, other FGA or quetiapine.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Gianfrancesco ²³⁶ 2002	Cohort	Claims databases for two mixed indemnity and managed health care plans	01/96-12/97	Any patient with an ICD-9 for psychosis. Exclude if: treated with AP for < 60 contiguous days; or if DM in 8 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA; or an ICD-9 of 250.xx during Tx or in 30 days post Tx.	Multiple logistic regression (UOA = Tx episode); Two models : 1) Tx duration; 2)AP dose (risperidone equivalents)	Concurrent AP use, age, gender, duration of observation, use of other psychotropics (\$), type of psychosis
Gianfrancesco ²³⁷ 2003	Cohort	Blue Cross/Blue Shield claims database	04/97-10/00	Any patient with an ICD-9 for psychosis; ID first Rx for an AP based on no previous Rx for that AP in preceding 90 days. Exclude if: treated with AP for < 60 contiguous days; or if DM in 8 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA; or Rx for insulin if accompanied by ICD-9 of 250.xx during Tx or in 30 days post Tx; or ICD-9 of 250.xx if accompanied by DM Rx.	Multiple logistic regression (UOA = Tx episode)	Age, gender, duration of treatment, use of other psychotropics (\$), type of psychosis, health care coverage, prior Tx for weight gain, use of β -blockers.
Gianfrancesco ²³⁸ 2003	Cohort	Claims databases for two mixed indemnity and managed health care plans	01/96-12/97	Any patient with an ICD-9 for MDD or BIP. ID first Rx for an AP based on no previous Rx for that AP in preceding 90 days. Exclude if: treated with AP but for <60 contiguous days; or if DM in 8 mo. pre-enrollment.	New-onset DM defined as: a new Rx for OHA; or an ICD-9 of 250.xx during Tx or in 30 days post Tx.	Multiple logistic regression (UOA = Tx episode)	Age, gender, duration of observation, use of other psychotropics, type of health care coverage, type of mood disorder, concurrent use of other AP.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Gianfrancesco ²³⁹ 2006	Cohort	Ohio Medicaid	01/99-03/03	Any patient with an ICD-9 for SCZ, manic D/O, BIP or MDD. ID first Rx for an AP based on no previous Rx for that AP in preceding 90 days. Exclude if: <2 contiguous Rx. for an AP; or if not enrolled for 8mo. prior to index date for episode; or if ICD-9 or Rx. for DM in 8mo. pre-index date.	New-onset DM defined as: a new Rx for OHA or insulin; or an ICD-9 of 250.xx during Tx (Design 1); and restricted to a new Rx. claim for DM in Design 2.	Multiple logistic regression (UOA = Tx episode)	Age, gender, duration of treatment, use of concomitant diabetogenic medication, mental health diagnosis, dose, substance abuse/dependence, prior use of statin, Hx of excess weight, switching of AP in preceding 60d.
Gianfrancesco ²⁴⁰ 2006	Cohort	Phar-Metrics Patient Centric database (patients from 40 private health plans in US).	01/99-04/02	Any patient with an ICD-9 for SCZ, BIP or MDD. ID first Rx for an AP based on no previous Rx for that AP in preceding 90 days. AP monotherapy only (Model 2). Exclude if: treated <2 contiguous Rx. for an AP; or if not enrolled for 8mo. prior to index date for episode; or if ICD-9 or Rx. for DM in 8mo. pre-index date (Model 2)..	New-onset DM defined as: a new Rx for OHA or insulin (Model 2),	Multiple logistic regression (UOA = Tx episode)	Age, gender, mental health diagnosis, duration of treatment, use of concomitant diabetogenic medication, substance abuse/dependence, AP dose, Hx of excess weight, switching of AP in preceding 90d, type of insurance coverage.
Kornegay ¹⁰ 2002	Nested Case-Control	UK General Practice Research database	01/94-12/98	Adults aged 18-64 who received an AP Rx. Exclude if: DM pre 01/1994; diagnosis of hyperglycemia but not DM; comorbid condition increasing likelihood of DM detection; <12 mo. recorded visits prior to 1st DM diagnosis. Controls matched 4:1 on age, gender, index date and general practice population.	Cases defined as new diagnosis in medical record if confirmed by follow-up information consistent with DM diagnosis.	Conditional logistic regression	BMI, smoking status, alcoholism, HTN, Hx of MI, stroke, angina; number of past AP Rxs, multiple AP use, primary psychiatry diagnosis, current use of: corticosteroid, lithium, thiazide, OCP.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Koro ³ 2002	Nested Case-Control	UK General Practice Research database	06/87-09/00	Any patient with a Dx of, and drug treatment for SCZ. Control defined as: ICD-9 for SCZ but no Dx of, or Rx for DM at any time. AP use defined as: ≥ 1 AP Rx within 3mo. of index date Exclude if: < 3 mo. follow-up; if case had Rx for DM in 3 mo. pre-index date.	Case defined as: ICD-9 of 250.xx; or a new Rx for OHA / insulin within 3mo. of AP use.	Conditional logistic regression	Age, gender, index year, duration of follow-up, use of α blockers, β blockers, thiazide, corticosteroids, phenytoin, OCP, valproate.
Kwong ⁴ 2002	Cohort	UK General Practice Research database	N/R	Any patient treated with an AP compared to general UK population.	N/R	Cox proportional hazard function	Age, gender, presence or absence of obesity.
Lambert ²²⁶ 2005	Case-Control	California Medicaid	01/95-09/00	Adults aged ≥ 18 diagnosed with SCZ (ICD-9 295.x) on ≥ 2 occasions, treated with ≥ 1 AP. Exclude if: exposure to both FGA and SGA; <6mo. continuous enrollment prior to index date for cases, prevalent DM; or not continually eligible during 12wks preceding DM Dx. Case: Developed DM subsequent to SCZ Dx. Control: SCZ patient without DM diagnosis at time of matching.	New-onset DM defined as: new ICD-9 of 250.xx on 2 different days; or a new Rx for OHA or insulin.	Conditional logistic regression	Age, ethnicity, use of concomitant diabetogenic medication, AP dose.
Lee ²⁴¹ 2002	Cohort	Protocare Sciences claims database for a managed care organization	09/97-12/99	Adults aged 18-65 treated with a FGA or SGA (include if ≥ 1 AP (concomitant or consecutive) after index date). Exclude if: <12mo continuous enrollment; or if Rx or ICD-9 for DM in 12mo. pre-index date or if ≥ 1 AP on index date.	New-onset DM defined as: a new Rx for OHA or insulin; or 2 ICD-9 of 250.xx on different days within 12 mo. of index date.	Multiple logistic regression	Age, squared age, gender, geographic region, mental health diagnosis, diagnosis of HTN or CVD, duration of AP Tx.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Leslie ²⁴² 2004	Cohort	Department of Veterans Affairs database	06/99-09/00	Schizophrenia patients on a stable regimen of AP for ≥3mo. Exclude if: OPD claim for DM; or <2 medical primary care visits in previous 6mo.	New-onset DM defined as: ICD-9 of 250.xx. Diabetic Ketoacidosis (DKA): hospitalization for DKA	Cox proportional hazard model	Age, gender, race, income, co-morbid mental health diagnoses, level of service use during stable period, degree of VA service-connected disability.
Lund ²⁴³ 2001	Cohort	Iowa Medicaid database	01/90-12/98	N/R	New-onset DM defined as: a new Rx for OHA or insulin; or ICD-9 of 250.xx.	Multiple logistic regression	Age, gender, duration of Tx
Micca ²⁵² 2006	Post-hoc analysis of 7 RCT	Olanzapine Clinical Trials Database	N/R	Pts ≥ 65 yrs with Alzheimer's disease or vascular dementia or combination of both. Exclude if: axis I D/O preceding dementia diagnosis; MMSE > 24; or DM at baseline (Dx of DM, Rx for DM. or casual blood glucose ≥200mg/dL).	New-onset DM defined as: clinical Dx for DM; Rx for OHA or insulin; 2x casual blood glucose ≥200mg/dL; or final random glucose ≥200mg/dL.	Cox proportional hazard model	Age, gender, nonwhite ethnicity, BMI, weight gain ≥7% from baseline, Hx HTN, baseline mean glucose ≥140mg/dL.
Miller ²⁴⁴ 2005	Cohort	Medstat Market Scan Database (U.S. private managed care health plans)	01/99-10/00	Any patient with mental health D/O (ICD-9: 290.00-312.99 or 331.00-331.99 excluding 305.1) with ≥ 30days for the same AP within a 3 mo. period. Exclude if: inpatient or OPD claim for DM between 01/99 and start of 3-mo. stable AP period.	New-onset DM defined as: ICD-9 for 250.xx after the index date.	ITT Cox proportional hazard model	Age, gender, mental health diagnosis, clinical comorbidity.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Moisan ²⁴⁵ 2005	Cohort	Régie de l'Assurance Maladie du Quebec database	01/97-08/99	Patients <65 yrs with ≥ 1 SGA Rx. Exclude if: Rx for an AP in 180 days pre-index date; ≥ 2 SGA on index date; Rx for clozapine or quetiapine; or not eligible for plan for 180 days pre-index date.	New-onset DM defined as: Rx for OHA or insulin.	Cox proportional hazard model	Age, gender, FGA use in 180 days preceding index date, type of beneficiary, number of physician visits per day of follow-up, use of concomitant diabetogenic medication.
Ollendorff ²⁴⁶ 2004	Cohort	PharMetrics Patient-Centric database (patients from 61 health plans in US)	09/96-06/01	Schizophrenia patients (≥ 1 medical claim for schizophrenia) treated with ≥ 1 AP Rx. Exclude if: > 1 AP on enrollment; if < 3 mo. follow-up data; if AP in 6 mo. pre-enrollment; or Hx DM in 12 mo. pre-enrollment.	New-onset DM defined as: ≥ 1 Rx for OHA or insulin; or ≥ 2 ICD-9 of 250.xx after the index date.	Cox proportional hazard function and multiple logistic regression	Age, gender, health plan, region, calendar year of initial treatment, number of DM screening tests/lab test overall, other mental health Dx, other medical Dx, total duration of therapy.
Østbye ²⁴⁷ 2004	Cohort	Advance PCS database (patients from 1171 health insurance plans)	06/00-05/02	AP group: Patients with ≥ 1 Rx for an AP. Control group one ≥ 1 Rx for an antidepressant but no AP Rx; Control group two: ≥ 1 Rx for an antibiotic and no AP or antidepressant Rx. Exclude if: Rx for other psychotropic during study period; Rx for DM in 6mo. pre-index date.	New-onset DM defined as: ≥ 1 Rx for OHA or insulin after the index date	Multiple logistic regression	Age, gender, Chronic Disease Score.
Sacchetti ²⁴⁸ 2005	Cohort	Italian Health Search Database	01/96-03/02	Any patient treated with haloperidol, olanzapine, quetiapine, or risperidone monotherapy. Exclude if: use of an AP during period prior to study entry; or DM at baseline.	New-onset DM defined as: a new Rx for OHA or insulin.	Cox proportional hazard model	Age, gender, duration of observation, time to development of DM, number of AP Rx.

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Study Type	Database	Timeframe	Inclusion / Exclusion	Dependent Variable	Statistical Methods	Covariates
Sumiyoshi ²⁴⁹ 2004	Cohort	OPD community health center, Tennessee	-05/02	Random sample of patients visiting OPD between 02/01 and 05/02 and currently taking clozapine, olanzapine, quetiapine or risperidone. Index date assigned as date current Tx. commenced. Exclude if. Dx of DM prior to index date.	N/R	Multiple logistic regression	Age, gender, race, duration of Tx.
Wang ²²⁷ 2002	Case-Control	New Jersey: Medicaid program; Pharmaceutical Assistance to the Aged Program; Medicare	01/90-06/95	Patients aged > 20 years with psychiatric diagnosis (recorded in 6mo pre-index date) and with 6mo. continuous enrollment. Cases: Index date= date of first Rx for DM with no Rx and no diagnosis of DM in 6 mo. pre-index date. Control: Index date frequency matched to control; no diagnosis or Rx for DM pre or post index date.	Case defined as: Rx for OHA or insulin..	Multiple logistic regression	Age, gender, others added in forward stepwise selection procedure p<0.2: SES, medication use, mental health diagnosis, other diagnosis, hospital days, OPD services, nursing home days.
Zhao ²⁵⁰ 2003	Cohort	IMS Health LifeLink Integrated Claims Solutions database	10/96-12/98	Schizophrenia patients 18-64 years (≥ 1 inpatient or ≥ 2 OPD diagnoses) with Rx for FGA or SGA and continuous enrollment for 12 mo. pre- and 24 mo. Post. Exclude if: Rx for AP in 6 mo. pre-enrollment; or DM in 12 mo. pre-enrollment.	New-onset DM defined as: Rx for OHA or insulin; or ≥ 2 ICD-9 of 250.xx in 12 mo. post index date.	Multiple logistic regression	Age, gender, regional differences, enrollment status, general health comorbidities (hyperlipidemia, HTN), other mental health Dx.)

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years	Diagnosis (%)	Mean Duration Tx (SD) Days	Mean Dose (SD) mg	Model Comparison
Barner 2003	White 69.9 Black 24.5 Hispanic 5.4 Other 0.3	All patients 94.3	59.0 (14.7) Age range (years) %: 18-39 5.6 40-49 20.0 50-59 35.0 60-69 10.6 ≥ 70 28.8	Schizophrenia 31.5 Bipolar Disorder 34.4 Depression 38.9 Substance Abuse 43.4 PTSD 16.1 Organic D/O 20.1 Other 61.4	N/R	N/R	<u>Compared to FGA</u> SGA Olanzapine Quetiapine Risperidone
Buse 2003	N/R	No AP 37 FGA 44 SGA 38	No AP 52 FGA 64 SGA 38 % Age distribution: 18-44 45-54 ≥65 No AP 36.5 39.3 24.2 FGA 20.8 26.0 53.2 SGA 30.2 23.6 46.3 Clozapine 6.8 25.3 37.9 Olanzapine 36.6 28.7 34.7 Quetiapine 35.8 28.1 36.0 Risperidone 24.6 19.2 56.2	N/R	No AP N/A FGA 7(74) Haloperidol 68(70) SGA 90(83) Clozapine 137(125) Olanzapine 89(85) Quetiapine 89(79) Risperidone 90(82)	Haloperidol 2.5(5.2) Clozapine 183.1(198.6) Olanzapine 5.1 (4.2) Quetiapine 79.9 (96.7) Risperidone 1.2(1)	<u>Compared to no AP</u> FGA SGA <u>Compared to Haloperidol</u> Clozapine Olanzapine Quetiapine Risperidone
Carlson 2002	N/R	General Population 47.2 FGA 40.8 SGA 44.5	General Population: 50(17) FGA: 58(22) SGA: 60(24) % Age distribution all pts: <45 45-64 ≥65 General 42.6 35.3 33.0 FGA 32.5 24.9 42.6 SGA 35.3 15.5 49.1	N/R	FGA 184(304) All SGA 264(332) Olanzapine 266(304) Risperidone 244(331)	N/R	<u>Compared to no AP</u> FGA SGA Olanzapine Risperidone <u>Compared to FGA</u> SGA <u>Compared to Risperidone</u> Olanzapine

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)			Gender (% Male)			Mean Age (SD) Years			Diagnosis (%)	Mean Duration Tx (SD) Days		Mean Dose (SD) mg	Model Comparison
Caro 2002	N/R			Olanzapine 49.7			% Age distribution all pts: <45 45-64 >65			N/R	N/R		N/R	<u>Compared to Risperidone</u> Olanzapine
				Risperidone 44			Olanzapine 57.3 25.0 17.8							
							Risperidone 41.2 19.9 38.9							
							% Age distribution SCZ pts:							
							Olanzapine 66.0 26.2 7.9							
							Risperidone 56.0 28.2 15.8							
Cavazzoni 2005	White 71.1	All 63.6				% Age distribution all pts:			Schizophrenia or related D/O	Olanzapine 123		N/R	<u>Compared to Olanzapine</u>	
	Non-White 28.9					New-onset DM 44.4 (10.3)				Risperidone 169			Non-olanzapine (FGA, risperidone, placebo)	
						Uncertain glucose tolerance 42.4 (11.4)				Clozapine 121				
						Normal glucose tolerance 37.1 (10.8)				Placebo 32				
										Haloperidol 43				
Citrome 2004	White 32	Cases 71	Cases 43.7 (12.8)				<u>Schizophrenia or schizoaffective D/O</u>			<u>SGA Tx.</u>	N/R		<u>Compared to FGA</u>	
		Controls 61	Controls 43.3 (11.4)				Cases 83			Cases 121.0(60.9)			Clozapine	
							Controls 83			Control 133.7(55)			Olanzapine	
													Quetiapine	
													Risperidone	
													>1 SGA	
Cunningham 2003	N/R			N/R			N/R			Schizophrenia	N/R		N/R	<u>Compared to FGA</u> SGA

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years	Diagnosis (%)	Mean Duration Tx (SD) Days	Mean Dose (SD) mg	Model Comparison
Etminan 2003	N/R	SGA 34.2 FGA 33.4	SGA 84.2(7.2) FGA 84.7(7.1)	N/R	N/R Mean number of Rx SGA 6.9 (5.1) FGA 6.5 (5.1)	N/R	<u>Compared to BZD</u> FGA SGA <u>Compared to Risperidone</u> Olanzapine Quetiapine
Farwell 2004	% Black: Olanzapine 45.1 Risperidone 47.9 FGA 47.9	Olanzapine 50.7 Risperidone 48.1 FGA 42.2	Olanzapine 42.9(12.0) Risperidone 42.4(14.5) FGA 42.6(14.9)	SCZ MDD DEM Other Olanzapine 35.2 17.1 6.2 24.9 Risperidone 22.6 18.5 9.3 22.4 FGA 0.2 5.0 1.6 8.9	N/R	N/R	<u>Compared to FGA</u> Olanzapine Risperidone
Feldman 2004	N/R	No AP 39.2 FGA 43.1 SGA 35.2 Clozapine 45.3 Olanzapine 34.2 Quetiapine 40.4 Risperidone 34.8	No Ap 72.1(8.3) FGA 78.4(9.1) SGA 79.2(8.8) Clozapine 75.2(7.2) Olanzapine 77.4(9.1) Quetiapine 76.9(8.5) Risperidone 80.4(8.8)	N/R	FGA 70.4(73.8) SGA 97.6(89.8) Clozapine 141.2(124.3) Olanzapine 102.0(96.1) Quetiapine 99.2(86.9) Risperidone 95.1(86.6)	Clozapine 114.0(160.1) Olanzapine 5.1(4.3) Quetiapine 95.5(83.4) Risperidone 1.2 (1.0)	<u>Compared to FGA</u> SGA Clozapine Olanzapine Quetiapine Risperidone
Fuller 2003	% Caucasian: All 73 Olanzapine 77 Risperidone 73 Haloperidol 66 Fluphenazine 63	100	All 50(14) Olanzapine 49(12) Risperidone 50(14) Haloperidol 51(15) Fluphenazine 47(10)	Schizophrenia 61 BIP 26 Depression 47 Dementia 8 Substance Abuse 58	N/R	Olanzapine 10.0(5.5) Risperidone 2.0(2.0) Haloperidol 5.0(8.7) Fluphenazine 10.0(9.7)	<u>Compared to Risperidone</u> Fluphenazine Haloperidol Olanzapine

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years	Diagnosis (%)						Mean Duration Tx (SD) Days	Mean Dose (SD) mg	Model Comparison
Gianfrancesco 2002	N/R	All untx 40.4	All untx 43(14.8)	<u>SCZ BIP MDD DEM Other</u>						All Tx 204(141)	<u>In Risperidone equivalents:</u>	<u>Compared to no AP</u>
		All Tx 39.1	All Tx 44(19.3)	All untx	10.4	52.1	34.3	6.8	5.8	Clozapine 282(165)		Olanzapine
		Olanzapine 37.8	Clozapine 40(14.1)	All Tx	17.2	21.5	38.8	6.4	16.2	Olanzapine 183(108)		Risperidone
		Risperidone 39.1	Olanzapine 43(16.9)	Olanzapine	22.4	24.8	37.8	2.1	12.8	Risperidone 204(144)		Clozapine
		Clozapine 41.3	Risperidone 43.0(20.7)	Risperidone	14.0	19.7	42.3	6.3	17.7	HPFGA 210(153)		HPFGA
		HPFGA 33.8	HPFGA 47.0(18.7)	HPFGA	16.6	20.1	36.9	8.6	17.7	LPFGA 210(156)		LPFGA
		LPFGA 31.5	LPFGA 46(20.5)	LPFGA	11.3	23.5	39.4	10.2	15.6			<u>Compared to Risperidone</u>
				Clozapine	57.1	19.0	14.3	0	9.5			Olanzapine
												Clozapine
												HPFGA
Gianfrancesco 2003	N/R	All untx 36	All untx 39.5(14.3)	<u>SCZ BIP MDD Other</u>						All Tx 297(294)	N/R	<u>Compared to no AP</u>
		All Tx 41	All Tx 37.5(15.1)	All untx	1	16	76	7		Olanzapine 270(267)		AP
		Olanzapine 43	Olanzapine 37.1(14.5)	All Tx	14	35	38	13		Quetiapine 225(189)		Olanzapine
		Quetiapine 35	Quetiapine 35.6(14.5)	Olanzapine	11	37	39	13		Risperidone 282(273)		Quetiapine
		Risperidone 45	Risperidone 33.4(16.3)	Quetiapine	10	37	43	10		FGA 369(360)		Risperidone
		FGA 36	FGA 43(12.6)	Risperidone	10	36	39	15				FGA
				FGA	18	32	36	14				
Gianfrancesco 2003	N/R	All untx 38.9	All untx 41.8(14.3)	<u>BIP MDD Manic</u>						All unTx 411(147)	<u>In Risperidone equivalents:</u>	<u>Compared to no AP</u>
		All Tx 31.8	All Tx 42.4(15.3)	All untx	48.1	39.7	12.2			All Tx 183(132)		Olanzapine
		Olanzapine 32.5	Olanzapine 42.7(15.5)	All Tx	30.6	64.5	4.9			Olanzapine 162(102)		Risperidone
		Risperidone 35.7	Risperidone 40(17.0)	Olanzapine	34.9	60.4	4.7			Risperidone 185(135)		HPFGA
		HPFGA 29.0	HPFGA 43.9(14.4)	Risperidone	27.1	68.2	4.7			HPFGA 195(141)		LPFGA
		LPFGA 26.8	LPFGA 42.7(15.5)	FGA	32.5	62.6	4.9			LPFGA 195(141)		

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years	Diagnosis (%)	Mean Duration Tx (SD) Days	Mean Dose (SD) mg	Model Comparison
Gianfrancesco 2006	White	75.0	All untx 27.3	All untx 40.0(18.2)			
	Black	23.5	FGA 41.4	FGA 50.4(15.7)			
	Hispanic	1.5	SGA 41.6	Clozapine 46.2(13.5)			
				Olanzapine 46.0(17.2)			
				Quetiapine 41.8(16.8)			
				Risperidone 44.2(19.4)			
				Ziprasidone 38.2(15.0)			
Gianfrancesco 2006	N/R		All untx 34.1	All untx 35.7(14.0)			
			FGA 35.2	FGA 41.0(13.7)			
			SGA 41.0	Olanzapine 36.1(15.0)			
				Quetiapine 34.7(14.6)			
				Risperidone 33.1(17.2)			
Kornegay 2002	N/R		All 41	Cases 51.4			

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)		Gender (% Male)	Mean Age (SD) Years				Diagnosis (%)			Mean Duration Tx (SD) Days		Mean Dose (SD) mg	Model Comparison		
Koro 2002	N/R		All ~ 37.5	% Age distribution all patients: <20 20-44 45-64 >65 Cases 0.4 16.4 42.4 40.8 Controls 0.5 16.3 43.0 40.2				Schizophrenia			Mean F/U period 5.2(3) years		N/R	<u>Compared to no AP</u> Olanzapine Risperidone <u>Compared to FGA</u> Olanzapine Risperidone		
Kwong 2002	N/R		N/R	N/R				N/R			N/R		N/R	<u>Compared to no AP</u> FGA SGA		
Lambert 2005	White	54.9	Cases 46.7	Cases	45.3(13.7)				Schizophrenia			N/R		<u>Low/Med/High %</u>	<u>Compared to FGA</u>	
	Black	17.1	Controls	Controls	45.3(13.3)										Clozapine	
	Hispanic	1.4	45.7											Clozapine	Olanzapine	
	Other	1.0												23.3/51.4/25.3	Quetiapine	
	Unknown	25.6												Olanzapine	Risperidone	
														17.2/31.3/51.5	>1 SGA	
														Quetiapine		
														34.4/36.6/29.0		
														Risperidone		
														20.0/49.9/30.1		
Lee 2002	N/R		All 45.1	All	45.1				<u>SCZ</u>	<u>BIP</u>	<u>MDD</u>	All	118.6	N/R	<u>Compared to FGA</u>	
			SGA 42.4	SGA	42.4				All	14.7	12.3	45.3	SGA	126.1		SGA
			FGA 46.3	FGA	46.3				SGA	15.0	15.1	52.2	FGA	108.3		Olanzapine
			Olanzapine 42.2	Olanzapine	42.2				FGA	14.3	8.6	35.9	Olanzapine	126.8		Risperidone
			Risperidone 42.7	Risperidone	42.7				Olanzapine	15.8	18.3	54.8	Risperidone	123.9		<u>Compared to Risperidone</u>
									Risperidone	14.4	12.7	49.9				Olanzapine

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years		Diagnosis (%)		Mean Duration Tx (SD) Days		Mean Dose (SD) mg	Model Comparison
Leslie 2004	N/R	N/R	N/R		Schizophrenia		N/R		N/R	<u>Compared to FGA</u> Clozapine Olanzapine Quetiapine Risperidone
Lund 2001	N/R	FGA 49.5 Clozapine 61.4	FGA 42.9(17.1) Clozapine 37.4(12.1)		Schizophrenia		FGA 735(807) Clozapine 765(732)		N/R	<u>Compared to FGA</u> Clozapine
Micca 2006	White 89.5	Olanzapine 33.4 Active Comparator 41.8 Placebo 45.4	Olanzapine 82.1(6.4) Active Comparator 80.4(7.0) Placebo 79.8(6.7)		Alzheimer's disease Vascular dementia Mixed/Vascular disease		151(101.1)		Olanzapine 4.87 (modal dose)	<u>Compared to Olanzapine</u> Active comparator (risperidone or FGA) Placebo
Miller 2005	N/R	All 43	All 40.4(16.8)		Adjustment Disorder	12	<u>Pts developing DM</u>	FGA 346.44		<u>Compared to FGA</u>
					Anxiety	25	FGA 321	Clozapine 434.47		Clozapine
					Alzh/DEM	8	Olanzapine 242	Olanzapine 10.83		Olanzapine
					BIP	28	Quetiapine 226	Quetiapine 211.93		Quetiapine
					Dysthymia	36	Risperidone 247	Risperidone 2.65		Risperidone
					MDD	47	<u>Pts NOT developing DM</u>			
					Other Psychoses	12	FGA 251			
					PTSD	4	Olanzapine 235			
					Schizophrenia	13	Quetiapine 170			
					Substance Abuse	8	Risperidone 284			

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years	Diagnosis (%)	Mean Duration Tx (SD) Days	Mean Dose (SD) mg	Model Comparison
Moisan 2005	N/R	51.5-51.6	% Age distribution all patients: 0-29 years: 20.4 30-44 years: 43.8 45-59 years: 29.9 60-64 years: 6.0	N/R	N/R Maximum follow-up 44mo.	N/R	<u>Compared to Risperidone</u> Olanzapine
Ollendorf 2004	N/R	FGA 48.6 SGA 48.0	FGA 42.4(11.7) SGA 38.0(12.4)	Schizophrenia <u>Comorbid Dx</u> SGA FGA BIP 43.6 31.3 Depression 53.2 37.6	FGA 485.0 (285.7) SGA 418.8 (247.2)	N/R	<u>Compared to FGA</u> SGA <u>Compared to Olanzapine</u> Clozapine Quetiapine Risperidone
Østbye 2004	N/R	FGA 52.0 SGA 55.4	FGA 57.0(21.2) SGA 42.3(27.5)	N/R	N/R	N/R	<u>Compared to FGA</u> SGA <u>Compared to Risperidone</u> Clozapine Olanzapine Quetiapine Ziprasidone
Sacchetti 2005	N/R	All 41.9 Haloperidol 40.7 Olanzapine 49.2 Risperidone 43.9 Quetiapine 37.6	Haloperidol 66.5(21.0) Olanzapine 52.6(20.4) Quetiapine 65.0(21.3) Risperidone 58.3(22.3)	N/R	Haloperidol 420.7(262.8) Olanzapine 301.7(221.8) Quetiapine 190.7(135.2) Risperidone 335.9(238.6)	N/R	<u>Compared to no AP and to Haloperidol*</u> Haloperidol Olanzapine* Quetiapine* Risperidone* <u>Compared to Risperidone</u> Olanzapine Quetiapine Olanzapine v. Quetiapine

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Ethnicity (%)	Gender (% Male)	Mean Age (SD) Years		Diagnosis (%)		Mean Duration Tx (SD) Days		Mean Dose (SD) mg	Model Comparison
Sumiyoshi 2004	% White: 70	All patients 66	All patients	42.9(10.6)	Schizophrenia spectrum D/O	54	Clozapine 1496(859)	N/R		<u>Compared to Olanzapine</u>
					Others	62	Olanzapine 578(545)			Clozapine
							Quetiapine 360(265)			Risperidone
							Risperidone 662(443)			<u>Compared to Clozapine</u>
										Risperidone
Wang 2002	% White: Cases 61.3 Controls 66.5	Cases 32.0 Controls 31.5	Cases Controls	63.6 (18.3) 61.9 (17.5)	Psychotic Affective Anxiety Other psychotic D/O	Cases Controls 40.3 39.7 29.1 27.4 12.8 14.0 45.4 42.9	N/R Range of use divided into 4 quartiles: 4-119, 120-158, 159-167, 168-176	N/R: Range divided into 4 quartiles: 17-225, 226-452, 453-572, 573-1618		<u>Compared to non-Clozapine AP</u>
										Clozapine
Zhao 2003	N/R	SGA 55.8 FGA 58.1 Olanzapine 57.4 Risperidone 54.6	SGA FGA Olanzapine Risperidone	44(11) 45(11) 44(11) 44(11)	Schizophrenia Comorbid/Prior Dx BIP Non-organic psychosis	SGA FGA 20.1 15.9 56.1 47.0	FGA 169(145) SGA 191(147) Olanzapine 193(143) Risperidone 185(151)	Olanzapine 9.96 (range 2.5-25) Risperidone 3.39 (range 0.5-12)		<u>Compared to FGA</u>
										SGA
										Olanzapine
										Risperidone

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence per 1000 pt-yrs (95% CI)	HR / RR (adjusted) /OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Barner 2003	FGA 147/1,973 Clozapine 2/21 Olanzapine 59/994 Quetiapine 15/216 Risperidone 51/705 Ziprasidone 1/7	N/R	N/R	No difference in incidence of DM between FGA and SGA (7.5 v. 6.6%, p=0.2907). No difference in incidence between SGA (Chi-squared: 2.1784, p=0.7030).	Covariates significantly related to the development of DM were age, minority race and preexisting hyperlipidemia. > 90% of population male.	Department of Veterans Affairs
Buse 2003	No AP 15.7(15.5-15.8) FGA 84(75-94) Haloperidol 85(70-100) SGA 67(62-72) Clozapine 67(16-188) Olanzapine 58(49-66) Quetiapine 39(27-51) Risperidone 79(71-87)	No AP 15.7(15.5-15.8) FGA 84(75-94) Haloperidol 85(70-100) SGA 67(62-72) Clozapine 67(16-188) Olanzapine 58(49-66) Quetiapine 39(27-51) Risperidone 79(71-87)	<u>Compared to No AP</u> FGA 3.5 (3.1 - 1.9) SGA 3.1 (2.9-3.4) Clozapine 3.3 (1.4-8.0) Olanzapine 3.0 (2.6-3.5) Quetiapine 1.7 (1.2-2.4) Risperidone 3.4 (3.1-3.8) <u>Compared to Haloperidol:</u> Clozapine 1.31 (0.60-2.86) Olanzapine 1.09 (0.86-1.37) Quetiapine 0.67 (0.47-0.97) <u>Compared to risperidone:</u> Olanzapine 0.90 (0.76-1.07)	Increased risk of DM with FGA and SGA v. no AP Tx. Risk of DM comparable for FGA and SGA. Among SGA, only risperidone associated with increased risk of DM v. to haloperidol. No difference in risk of DM between olanzapine and risperidone. Dose response relationship (per quartile of observed dose) observed for thioridazine (HR: 2.6; 2.9; 2.9; 4.3) and possibly quetiapine (HR: 1.8; 1.4; 0.6; 3.1).	Mean Tx doses low but wide range of doses used. Across all agents older patients prescribed lower doses (consistent across all quartiles). Increasing age associated with significant increase in risk of DM.	Eli Lilly and Company
Carlson 2005	No AP 33,536/1,291,548 FGA 230/59,089 SGA 64 /9,053 Olanzapine 17/2,374 Risperidone 37 /5,213	No AP 3.31(3.27-3.35) FGA 7.7(6.7-8.7) SGA 9.8(7.4-12.2) Olanzapine 9.8(5.1-14.5) Risperidone 10.6(7.4-12.2)	<u>Compared to no AP:</u> FGA 1.9 (1.6 – 2.3) SGA 2.9 (2.0-4.4) Olanzapine 3.9 (1.8-8.1) Risperidone 2.5 (1.4-4.5) <u>Compared to FGA</u> SGA 1.6 (1.0-2.5) <u>Compared to Risperidone</u> Olanzapine 1.5 (0.6-3.9)	Increased risk of DM with FGA, any SGA, olanzapine or risperidone v. no AP Tx. Increased risk of DM with SGA v. FGA. No difference in risk of DM between olanzapine and risperidone.	Obesity and increasing age associated with significant increase in risk of DM. Study controlled for duration of Tx.	Eli Lilly

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence per 1000 pt-yrs (95% CI)	HR / RR (adjusted) /OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Caro 2003	Olanzapine 319 /19,153 Risperidone 217 /14,793	Olanzapine 17 Risperidone 16	<u>Compared to risperidone:</u> Olanzapine 1.2 (1.00-1.43) <u>Stratifying by Drug Exposure Time Risk compared to risperidone:</u> <3 mo. 1.90 (1.40-2.57) 3<6 mo. 1.16 (0.75-1.78) 6<12 mo. 1.11 (0.81-1.510) ≥12mo. 1.06 (0.86-1.31)	Increased risk of DM with olanzapine v. risperidone. Relative risk decreased with increasing drug exposure time, with greatest risk noted for drug exposure time <3mo. Increased risk of DM for female olanzapine pts. v. female risperidone pts (HR 1.30(1.05-1.65)). Dx of schizophrenia not a significant predictor of DM.	> 1 Rx dispensed to 89.5% of olanzapine pts and to 82.9% of risperidone pts. Olanzapine pts. younger, more frequently male, more likely to have a Dx of schizophrenia (62% v 39%) and to be co-prescribed haloperidol (38.1% v 32.6%).	Janssen Ortho Inc
Cavazzoni 2005	Placebo 3/206 Haloperidol 9/1,164 Clozapine 33/211 Olanzapine 71/3,068 Risperidone 5/3646	N/R	<u>Compared to olanzapine:</u> Pooled group (haloperidol/, placebo, risperidone) 1.46 (0.83-2.57)	No difference in risk of DM between olanzapine and a pooled cohort of patients receiving haloperidol, risperidone or placebo.	Short term studies – median exposure duration < 6mo. Significant increase in risk of DM with: elevated blood glucose at baseline; presence of multiple risk factors for DM.	Eli Lilly and Company
Citrome 2004	Cases Controls FGA 17 250 Clozapine 24 171 Olanzapine 43 402 Quetiapine 24 112 Risperidone 31 305 >1 SGA 42 208	N/R	<u>Compared to FGA:</u> Clozapine 2.06(1.07-3.99) Olanzapine 1.57(0.87- 2.82) Quetiapine 3.09(1.59-6.03) Risperidone 1.50(0.81-2.79) >1 SGA 2.86(1.57-5.2)	Increased risk of DM with clozapine, quetiapine or >1 SGA compared to an FGA alone.	Patients not limited to monotherapy – could receive concurrent FGA with SGA. Increased monitoring frequency observed for clozapine, olanzapine, and >1 SGA.	Nathan S. Kline Institute for Psychiatric Research
Cunningham 2003	Total 719 /12,235	N/R	<u>Compared to FGA:</u> Clozapine 1.48(0.65-3.37) Olanzapine 1.27(1.04-1.56) Quetiapine 3.34 (2.51-4.45) Risperidone 1.49(1.22-1.81)	Increased risk of DM with olanzapine, quetiapine and risperidone v. FGA.	Conducted case-control study also with 4:1 matching by age, sex, year and VA facility with similar results.	Department of Veterans Affairs

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence per 1000 pt-yrs (95% CI)	HR / RR (adjusted) /OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Etminan 2003	SGA 3,250 FGA 1,888 BZD 5,326 Olanzapine 13/615 Quetiapine 1/101 Risperidone 48/2,274	SGA 31 FGA 47 BZD 40 Corticosteroid 190	<u>Compared to BZD:</u> SGA 0.89(0.66-1.21) FGA 1.27(1.41-3.12) <u>Compared to Risperidone (unadj.):</u> Olanzapine 1.00 Quetiapine 0.68	No increase in risk of DM with SGA or FGA compared to BZD. Comparable risks of DM for olanzapine, risperidone and quetiapine.	Older population with expected under-representation of schizophrenic pts. Covariates associated with an increased risk of DM were: increasing age; antiepileptic Rx; low income; and # drugs used.	Canadian Institute of Health Research
Farwell 2004	Olanzapine 35/438 Risperidone 17/482 FGA 70/2,195		<u>Compared to FGA:</u> Olanzapine 1.9(1.1-1.3) Risperidone 0.7(0.4-1.4)	Increased risk of DM with olanzapine but not risperidone v. FGA even after controlling for weight gain. DM not related to weight gain but significant risk of DM with baseline obesity.	Used ITT approach. Schizophrenia, dementia and drug/alcohol use not related to DM risk. Urban indigent clinic population.	Bristol-Myers Squibb
Feldman 2004	FGA 238 /11,546 SGA 515/19,407 Clozapine 5/117 Olanzapine 142/5,382 Quetiapine 29/1,664 Risperidone 339/12,244	N/R	<u>Compared to no AP</u> FGA 3.6(3.1-4.1) SGA 3.5(3.2-3.8) Clozapine 3.1(1.0-9.5) Olanzapine 3.6(3.0-4.2) Quetiapine 1.9(1.3-2.9) Risperidone 3.7(3.3-4.2) <u>Compared to FGA* or Haloperidol:</u> SGA* 1.1(0.9-1.3) Clozapine 1.4(0.6-3.5) Olanzapine 1.2(0.9-1.5) Quetiapine 0.7(1.5-1.1) Risperidone 1.2(1.1-1.6)	Compared to haloperidol risk of DM increased with risperidone among all patients, and those aged ≥75 years; and with quetiapine in patients aged 60-74 years only. Risk of DM increased for each AP v. no AP.	Short Tx. Duration (2.5-3 mo.). Low-dose Tx in elderly population.	Eli Lilly
Fuller 2003	Total 386 /5,837 Olanzapine 3,056 Risperidone 2,493 Haloperidol 1,790 Fluphenazine 428	N/R	<u>Compared to Risperidone:</u> Olanzapine 1.37(1.06-1.76) Haloperidol 0.89(0.67-1.17) Fluphenazine 1.11(0.68-1.79)	Increased risk of DM with olanzapine v. risperidone. Median time to development of DM: 11mo. (1 day-52mo).	Controlled for drug switching patterns: % receiving agent as initial Tx: Risperidone 73.7 Olanzapine 70.3 Haloperidol 86 Fluphenazine 71.8	Janssen Pharmaceutica

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence /1000 pt-yrs (95% CI)	HR / RR (adjusted)/OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Gianfrancesco 2002	*At 12 mo. observation All unTx 34 /3,061 All Tx 67 /4,334 Olanzapine 25 /1,047 Risperidone 10 /1,368 HPFGA 20 /1,376 LPFGA 9 /486 Clozapine 3 /63	N/R	<u>Compared to unTx at 12 mo.:</u> Olanzapine 3.10(1.62-5.93) Risperidone 0.88(0.37-2.07) HPFGA 2.13(1.10-4.13) LPFGA 3.46(1.52-7.78) Clozapine 7.44(1.60-34.75) <u>Compared to risperidone at 12mo.:</u> Olanzapine 3.53 Clozapine 8.45	Increased risk of DM with olanzapine and clozapine, but not risperidone v. unTx pts. Increased risk of DM with clozapine and olanzapine v. risperidone. Dose-response for olanzapine (2.6mg increase in olanzapine \equiv increased OR of DM of 1.22) but not for risperidone or clozapine.	Two logistic regression models developed based on dose and Tx. duration. Data subsequently extrapolated to 12 mo. duration. Covariates significantly associated with increased risk of DM were: increasing age and use of non AP psychotropics. Type of psychosis was not related to the outcome.	Janssen Pharmaceutica
Gianfrancesco 2003	*At 12 mo. Observation All unTx 87 /10,296 All Tx 30 /6,582 Olanzapine 15 /2,703 Quetiapine 3 /922 Risperidone 5 /2,860 FGA 7 /2,756	N/R	<u>Compared to unTx at 12 mo*:</u> Olanzapine 1.43 (1.05-1.96) Quetiapine 0.976 (0.42-2.27) Risperidone 0.660 (0.31-1.41) FGA 1.05 (0.67-1.61)	Increased risk of DM for patients treated with olanzapine but not risperidone, quetiapine or FGA v. unTx. Pts.	30% of patients had > 1 Tx episode with the same or different AP. Overlap of Tx episodes occurred in 27% of observations Covariates significantly associated with increased odds of DM were: age; β blocker Rx; and Tx duration. Dx of BIP or MDD were associated with a lower odds of DM compared to 'other psychosis.	AstraZeneca Pharmaceuticals
Gianfrancesco 2003	Total 66 /5,723 All unTx 2,644 All Tx 2,592 Olanzapine 656 Risperidone 849 HPFGA 785 LPFGA 302	N/R	<u>Compared to unTx at 12 mo.:</u> Olanzapine 4.289 (2.10-8.83) Risperidone 1.02 (0.35-3.01) HPFGA 1.94 (0.79-4.79) LPFGA 4.97 (1.97-12.61) <u>Compared to risperidone at 12mo.:</u> Olanzapine 4.19** HPFGA 1.90 LPFGA 4.85**	Increased odds of DM with olanzapine and LPFGA v. unTx patients. Increased odds of DM with olanzapine and LPFGA v. risperidone. Dose response relationship seen with olanzapine 2.6mg increase in olanzapine \equiv increased OR of DM of 1.31) but not risperidone or FGA.	15% of patients had >1 Tx episode with overlapping Tx. episodes in 20% of observations. Concurrent AP use documented as follows: risperidone 17.1%; olanzapine 18.9%; HPFGA 15.0% and LPFGA 19.5%. Covariates significantly associated with an increased odds or DM were: age; observation period and use of other psychotropics.	AstraZeneca Pharmaceuticals

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence /1000 pt-yrs (95% CI)	HR / RR (adjusted)/OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Gianfrancesco 2006	>8- <12 mo. observation All unTx 190/8,589 FGA 61/890 Clozapine 4/48 Olanzapine 92/1,567 Quetiapine 38/965 Risperidone 80/1,632 Ziprasidone 4/112	N/R	<u>Compared to unTx –Design 2</u> FGA 0.885(0.785-0.997) Clozapine 1.272(1.024-1.579) Olanzapine 1.001(0.894-1.120) Risperidone 0.920(0.824-1.028) Ziprasidone 0.673(0.438- 1.036) <u>Compared to unTx –Design 3:</u> FGA 1.484(1.138-1.934) Clozapine 1.124(0.983-1.284) Olanzapine 1.149(1.001-1.319) Risperidone 1.124 (0.983-1.248) Ziprasidone 0.717 (0.415- 1.239)	Increased odds of DM with clozapine and decreased risk with FGA v. unTx patients using Design 2 (ICD-9 or Rx. for DM). Increased odds of DM with olanzapine and clozapine v. unTx patients using Design 3 (Rx. for DM only). Increased odds of DM with medium or high dose AP v. no Tx or low dose AP (10-25%). Lower risk of DM with SCZ or BIP v. MDD.(15-20%).	Study examined for selection bias-authors conclude that after 01/01 risperidone more likely and olanzapine less likely to be prescribed to patients at risk of DM. Covariates significantly associated with increased odds of DM were: increasing age; non-white race, baseline excess weight, statin use, substance use, and increasing observation period.	AstraZeneca Pharmaceuticals
Gianfrancesco 2006	Frequency (%) of DM adjusted for duration All unTx 0.98 FGA 3.38 Olanzapine 2.67 Quetiapine 1.05 Risperidone 1.33	N/R	<u>Compared to unTx. (Model 2):</u> FGA 1.755(1.381-2.221) Olanzapine 1.858(1.549-2.238) Quetiapine 1.087(0.742-1.612) Risperidone 1.224(0.962-1.562)	Increased odds of DM with olanzapine and FGA (but not quetiapine or risperidone) v. unTx patients. Increased odds of DM with high dose risperidone, medium and high dose olanzapine and all doses of FGA v. unTx patients.	Covariates significantly associate with increased odds of DM: age, excess weight at baseline, use of beta-blockers. Increased odds of DM with SCZ Dx v. MDD (40-100%) and v. BIP (30-70%).	N/R
Kornegay 2002	Total 73,428 Cases 424 Controls 1,522 Past AP (Cases) 238 Recent AP (Cases) 26 Current AP SGA (cases) 8 FGA(cases) 152	N/R	<u>Compared to Past exposure (none in 12mo.):</u> Current SGA 4.7 (1.5-4.9) Current FGA 1.7 (1.2 to 2.3) Recent FGA 1.0 (0.6-1.6)	Increased odds of DM with current, but not recent use of SGA or FGA v. no AP Tx.	Very small N for SGA (N=8 Case; N=8 Control). No mental health diagnosis independently associated with increased odds of DM. Covariates significantly associate with increased odds of DM: increasing BMI; Hx of HTN and Hx of previous MI.	FDA and Boston Collaborative Drug Surveillance Program

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence /1000 pt-yrs (95% CI)	HR / RR (adjusted)/OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Koro 2002	Total 19,637 DM: Cases 451 Controls 2,696 <u>≥ 1 Rx (DM Cases):</u> FGA non depot 235/17,320 FGA depot 48/4,421 Olanzapine 9/970 Risperidone 15/1,683 Other SGA 1/578	All treated pts 4.4 Women 5.3 Men 3.5 <u>Within 3mo. Of Rx:</u> Olanzapine 10.0(5.2-19.2) Risperidone 5.4(3.0-9.8) FGA 5.1(4.5-5.8)	<u>Compared to no Tx at 3mo.:</u> FGA 1.4 (1.1-1.7) Olanzapine 5.8 (2.0-16.7) Risperidone 2.2 (0.9-5.2) Other SGA 1.6 (0.2-17.1) <u>Compared to FGA at 3mo.:</u> Olanzapine 4.2 (1.5-12.2) Risperidone 1.6 (0.7-3.8) Other SGA 1.2 (0.1-12.4)	Increased odds of DM within 3mo. of index date for patients with SCZ taking olanzapine or FGA v. unTx pts. Increased odds of DM for patients taking non-depot FGA or olanzapine v. all other Tx pts. Increased odds of DM with olanzapine but not risperidone within 3mo. of index date v. FGA.	New SGA included: amisulpiride; remoxipride; sertindole. Pts may have taken > 1 AP in study period. Very small N when limited to pts Tx with monoTx AP within 3 mo. of index date.	Bristol-Myers Squibb
Kwong 2002	General 266,272 FGA 43,561 SGA 2,550 Olanzapine 535 Risperidone 1,811	N/R	<u>Compared to general population:</u> FGA 1.3 (1.003-1.8) SGA 3.3 (1.7-6.5) <u>Compared to FGA:</u> SGA 2.6 (1.3-5.3)	Increased risk of DM with FGA and SGA v. general population. Increased risk of DM with SGA v. FGA.		Eli Lilly and Company
Lambert 2005	Cases 3,663	N/R	<u>Compared to FGA:</u> Clozapine 1.3(1.2-1.5) Olanzapine 1.4 (1.2-1.5) Quetiapine 1.9(0.9-4.1) Risperidone 1.0(0.9-1.2) >1 SGA 1.6(1.3-1.9)	Using 12, 24 or 52-week exposure windows, odds of DM increased with olanzapine, clozapine or combination SGA v. FGA. Possible dose-response relationship with olanzapine using 52-week exposure window.	Did not use an AP wash-out period. Small Tx. numbers for quetiapine. Dose-strata based on empirical distribution and clinical judgment. Black or Unknown race, and use of certain concomitant diabetogenic medications associated with increased odds of DM.	Bristol-Myers Squibb
Lee 2002	Total N within 12mo.: Total 71 /2,315 FGA 31 /981 SGA 40 /1,334 Olanzapine 13 /513 Risperidone 25 /750	N/R	<u>Compared to FGA:</u> SGA 1.01 (0.612-1.668) Olanzapine 0.864 (0.431-1.732) Risperidone 1.074 (0.612-1.885) <u>Compared to Risperidone:</u> Olanzapine 0.786 (0.384-1.610)	No difference in odds of DM between SGA, olanzapine or risperidone v. FGA. No difference in odds of DM between olanzapine and risperidone.	Did not control for dual-AP Tx or consecutive AP after the index drug (ITT methodology); however >75% pts exposed to only the index AP. Tx duration, Hx of HTN and Hx of CVD associated with increased risk of DM; decreased risk of DM with BIP and West South Central region.	Eli Lilly and Company

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence /1000 pt-yrs (95% CI)	HR / RR (adjusted)/OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Leslie 2004	Total 4,132/56,849	All 4.4	<u>Compared to FGA:</u> Clozapine 1.57(1.31-1.89) Olanzapine 1.15(1.07-1.24) Quetiapine 1.20(0.99-1.44) Risperidone 1.01(0.93-1.10)	Increased risk of DM with clozapine and olanzapine v. FGA. Increased risk of DKA with clozapine and olanzapine v. FGA in entire sample, but no difference in risk when sample limited to DM patients.	ITT approach: patients followed for up to 25 mo. with risk assessment based on AP Rx in first stable 3mo. period. AP switch rate 17% overall and similar across agents. Increased risk of DM with clozapine and olanzapine apparent after ≥12mo. follow-up only.	Department of Veterans Affairs, National Institute of Mental Health, Bristol-Myers Squibb
Lund 2001	Total 2,827 FGA 78 /2,296 Clozapine 21 /531	N/R	<u>Compared to FGA:</u> Clozapine 1.16 <u>Compared to FGA (20-34 yr):</u> Clozapine 2.5 (1.2-5.4)	Similar incidence of DM, HTN and hyperlipidemia for clozapine and FGA. Increased risk of DM and hyperlipidemia (but not HTN) in patients aged 20-34 years Tx with clozapine v. FGA.	Using similar time periods, incidence of DM in patients aged 20-34 years in this database was 1.7% (1.6-1.9).	Iowa Medicaid Drug Utilization Review Committee
Micca 2006	All 29/1,398 Olanzapine 19 /835 Risperidone/FGA 4 /223 Placebo 6 /340	N/R	<u>Compared to olanzapine:</u> Risperidone/FGA p=0.76 Placebo p=0.82	No difference in risk of DM in elderly dementia patients between olanzapine, an active comparator (risperidone/FGA) or placebo. Olanzapine associated with increase in uncertain glucose tolerance v. placebo (p=0.008).	Study also examined 'uncertain glucose tolerance.' Elevated casual glucose (≥140mg/dL) the only significant risk factor for new-onset DM.	Eli Lilly
Miller 2005	All 339/7,381 FGA 145 /1,981 Clozapine 7 /84 Olanzapine 93 /1,986 Quetiapine 24 /775 Risperidone 70 /2,555	N/R	<u>Compared to FGA:</u> Clozapine 1.222(0.563-2.652) Quetiapine 0.740(0.726-1.236) Risperidone 0.690(0.514-0.925)	Decrease in risk of DM with risperidone v. FGA. No difference in risk of DM between other SGA v. FGA. Stratifying by gender, decrease in risk of DM for men Tx. with quetiapine or risperidone only v. FGA.	Annual incidence DM: 4.7%. ITT approach – risk based on AP used during first ID stable period. Pt could subsequently switch Tx; (rate 13.3%) or use dual-Tx. Increased risk of DM with diagnosis of SCZ; BIP or PTSD. Risk decreased for other psychoses. Increased risk of DM with increase in age or clinical comorbidity.	Department of Veterans Affairs and National Institute of Mental Health

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence /1000 pt-yrs (95% CI)	HR / RR (adjusted)/OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Mosian 2005	(x10 ⁻⁵ /days) Olanzapine 4.45 Risperidone 3.14	N/R	<u>Compared to risperidone:</u> Olanzapine 1.33(1.03-1.73)	Increase in risk of DM with olanzapine v. risperidone.	Also examined risk of new-onset dyslipidemia and combined risk of new-onset dyslipidemia and DM – significant increase in risk in both cases with olanzapine v. risperidone.	Janssen - Ortho
Ollendorf 2004	Within 12mo.: FGA 17 /617 SGA 45 /1,826 Clozapine 2 /35 Olanzapine 23 /937 Quetiapine 4 /164 Risperidone 16 /690	N/R	<u>Compared to FGA:</u> SGA 1.172(1.061-1.30) <u>Compared to olanzapine:</u> Clozapine 1.467(0.930-1.168) Quetiapine 1.170(0.967-1.372) Risperidone 1.049(0.930-1.168)	Increase in risk of DM with SGA v. FGA. No difference in risk of DM between different SGA.	Significant positive association between year of commencing AP and odds of DM (possibly related to increased surveillance).	N/R
Østbye 2004	Within 12mo.: FGA 52/4,607 SGA 77/10,265 Clozapine 1/127 Olanzapine 31/3,190 Quetiapine 6/1,111 Risperidone 29/4,859 Ziprasidone 1/69	FGA 11.3 SGA 7.5 Clozapine 7.9 Olanzapine 9.4 Quetiapine 5.4 Risperidone 6.0 Ziprasidone 6.0	<u>Compared to FGA:</u> SGA 0.86(0.60-1.23)) <u>Compared to risperidone:</u> Clozapine 1.13(0.15-8.37) Olanzapine 1.34(0.83-2.15) Quetiapine 0.66(0.28-1.57) Ziprasidone 2.64(0.35-19.90)	No difference in risk of DM between FGA and SGA. No difference in risk of DM between clozapine, olanzapine, quetiapine or ziprasidone v. risperidone.	Small treatment numbers of clozapine and ziprasidone. Increasing age, male gender and Chronic Disease Score associated with increased odds of DM.	Eli Lilly
Sacchetti 2005	All unTx 8 /6,026 Haloperidol 33 /2,071 Olanzapine 4 /226 Quetiapine 3 /109 Risperidone 9 /567	All unTx 1.5 Haloperidol 19.6 Olanzapine 22.8 Quetiapine 52.7 Risperidone 24.9	<u>Compared to unTx:</u> Haloperidol 12.40(6.27-24.52) Olanzapine 20.35(6.86-60.33) Quetiapine 33.68(9.18-123.55) Risperidone 18.71(8.18-42.81) <u>Between AP</u> No significant comparison between any pair of individual AP agents.	Increased odds of DM with haloperidol, olanzapine, quetiapine or risperidone v. untreated patients. No difference in risk of DM between haloperidol and any SGA, or between SGA.	Lack of balance in group sizes. Followed patients for a maximum of 2 years.	Health Association of Lombard Region (Italy)

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Author (Year)	Incidence (N) / Treatment (N)	Incidence /1000 pt-yrs (95% CI)	HR / RR (adjusted)/OR (adjusted) (95% CI)	Conclusions	Comments	Affiliation
Sumiyoshi 2004	Total 14/116 Clozapine 5/23 Olanzapine 5/55 Quetiapine 0/15 Risperidone 4/23	N/R	<u>Compared to olanzapine:</u> Clozapine 0.836 (0.467-1.495) Risperidone 0.759 (0.346-1.668) <u>Compared to clozapine:</u> Risperidone 0.898 (0.135-5.994)	No difference in odds of DM between clozapine, olanzapine and risperidone. No difference in time to onset of DM between clozapine, olanzapine and risperidone.	Small study – total 116 patients. Study permitted combination AP.	National Institutes of Health Diabetes Research and Training
Wang 2002	<u>Cases Controls</u> All 7,227 6,780 Clozapine 94 115 Other AP 2,414 2,400	N/A	<u>Compared to no AP:</u> Clozapine 0.78(0.59-1.02) Non-clozapine AP 0.92(0.86-0.98) <u>Compared to no AP by dose quartile:</u> 17-225mg 1.67 (0.75-3.76) 226-452mg 2.03 (0.91-4.55) 453-572mg 0.71 (0.31-1.63) 573-1618mg 0.85 (0.38-1.91)	No increase in risk of DM with clozapine compared to no AP. No association between increased dose or duration of clozapine and odds of DM.	Poor statistical power to detect an effect (# cases > #controls).	NIHM grant
Zhao 2003	Overall 815 FGA 5 /353 SGA 13 /462 Olanzapine 4 /258 Risperidone 8 /187	N/R	<u>Compared to FGA:</u> SGA 2.353 (0.802-6.896) Olanzapine 1.059 (0.261-4.302) Risperidone 4.061 (1.230-13.40) <u>Compared to Risperidone:</u> Olanzapine 0.267 (0.072-0.988)	Increased odds of DM with olanzapine v. risperidone. Increased odds of DM with risperidone, but not olanzapine or SGA (as a group) v. FGA.	Covariates associated with an increased risk of DM were age and preexisting hyperlipidemia.	Eli Lilly and Company

Appendix B: Comparison of Database Studies Examining the Association between Antipsychotic Use and New-Onset Diabetes (continued)

Abbreviations:		
<i>Adj D/O - Adjustment disorder</i>	<i>ID - Identify</i>	<i>Rx - Prescription</i>
<i>Alzh - Alzheimer's Disease</i>	<i>ITT - Intention-to-treat</i>	<i>RR - Relative risk</i>
<i>AP - Antipsychotic</i>	<i>ICD-9 - International classification of disease, 9th edition</i>	<i>SCZ - Schizophrenia</i>
<i>BIP - Bipolar disorder</i>	<i>LPFGA - Low potency first-generation antipsychotic</i>	<i>SGA - Second-generation antipsychotic</i>
<i>CVD - Cardiovascular disease</i>	<i>MDD - Major depressive disorder</i>	<i>SES - Socio-economic status</i>
<i>DEM - Dementia</i>	<i>Mo. - Month</i>	<i>SD - Standard deviation</i>
<i>DM - Diabetes Mellitus</i>	<i>MI - Myocardial infarction</i>	<i>Tx - Treatment</i>
<i>D/O - Disorder</i>	<i>N/R - Not recorded</i>	<i>T2DM - Type 2 diabetes mellitus</i>
<i>Dx - Diagnosis</i>	<i>OBS - Organic brain syndrome</i>	<i>UK - United Kingdom</i>
<i>FGA - First-generation antipsychotic</i>	<i>OHA - Oral hypoglycemic agent</i>	<i>Unadj - Unadjusted</i>
<i>HPFGA - High potency first-generation antipsychotic</i>	<i>OPD - Out-patient department</i>	<i>Untx - Untreated</i>
<i>HR - Hazard ratio</i>	<i>OR - Odds ratio</i>	<i>UOA - Unit of Analysis</i>
<i>HTN - Hypertension</i>	<i>Pts - Patients</i>	<i>VA - Veterans affairs</i>
<i>Hx - History</i>	<i>PTSD - Post traumatic stress disorder</i>	<i>Yrs - Years</i>

Appendix C: Detailed Description of Study Variables

Variable	Definitions	Categories	Comments
DEPENDENT VARIABLES			
Prevalence of diabetes	Diagnosis of diabetes based on one of the following occurring during the patient follow-up period: ➤ Medical claim with ICD-9 for diabetes (ICD-9: 250.00-250.99) ➤ Treatment with an antidiabetic medication	Categorical variable 0 = No diabetes 1 = Diabetes	Recorded as percentage of cases among eligible enrollees
Incidence of diabetes	New diagnosis of diabetes based on one of the following occurring at least seven days subsequent to the index date, with no history of diabetes in the 180 days preceding the index date: ➤ Medical claim with ICD-9 for diabetes (ICD-9: 250.00-250.99) ➤ Treatment with an antidiabetic medication	Categorical variable 0 = No diabetes 1 = Diabetes	Any case occurring less than 30 days subsequent to treatment discontinuation was considered an incident case Recorded as percentage of cases among eligible enrollees
Adherence to antipsychotic therapy	Adherence defined as mean Medication Possession Ratio (MPR)	Continuous variable	Excluded if patient did not have at least one prescription refill
Persistence with antipsychotic therapy	Persistence defined as the sum of the number of persistent days Persistent days defined as the number of continuous days therapy, that is, refill within (number of days supplied x 1.5)	Continuous variable	Excluded if patient did not have at least one prescription refill
Time to occurrence of diabetes	Length of time in days between the date of the index antipsychotic prescription and the date of first diagnosis of diabetes	Continuous variable	Excluded if occurred within seven days of the index date

Appendix C: Detailed Description of Study Variables (continued)

Variable	Definitions	Categories	Comments
INDEPENDENT VARIABLES			
Demographic variables			
Age	Participant's age in years at the index date	Continuous variable	
Gender		Categorical variable 0 = Female 1 = Male	
Race / Ethnicity		Categorical variable 1 = White 2 = African American 3 = Hispanic 4 = Native American 5 = Asian American 6 = 'Other'	
Clinical variables			
Hypertension	Diagnosis of hypertension based on a medical claim with ICD-9 for hypertension (ICD-9: 401.x-405.x)	Categorical variable 0 = No hypertension 1 = Hypertension	
Dyslipidemia	Diagnosis of dyslipidemia based on a medical claim with ICD-9 for dyslipidemia (ICD-9: 272.0-272.4).	Categorical variable 0 = No dyslipidemia 1 = Dyslipidemia	

Appendix C: Detailed Description of Study Variables (continued)

Variable	Definitions	Categories	Comments
Clinical variables continued			
Primary Mental Disorder Diagnosis	<p>Diagnoses classified based on ICD-9 codes assigned for medical claims and then categorized according to the following rules. If patient had a diagnosis of:</p> <ul style="list-style-type: none"> ➤Schizophrenia or bipolar disorder then this considered the primary diagnosis ➤Both schizophrenia and bipolar disorder then patient classified according to the modal diagnosis. If both diagnoses occurred with equal frequency then the diagnosis closest to the study endpoint used as the primary diagnosis. ➤Both ‘other psychotic disorder’ and ‘other non-psychotic disorder’ then ‘other psychotic disorder’ considered the primary diagnosis. ➤Both ‘other psychotic disorder’ and dementia then ‘other psychotic disorder’ considered to be the primary diagnosis. ➤Both dementia and ‘other non-psychotic disorder’ then dementia considered the primary diagnosis. 	<p>Categorical variable</p> <p>0 = Schizophrenia</p> <p>1 = Bipolar disorder</p> <p>2 = Other psychotic disorder</p> <p>3 = Dementia</p> <p>4 = Other non-psychotic mental disorder</p>	<p>Excluded if:</p> <p>Primary diagnosis was mental retardation (ICD-9: 317.x-319.x)</p>
Medication Variables			
Antipsychotic Class	<p>Index prescription classified as first-generation or second-generation antipsychotic</p> <p>Index prescription defined as first antipsychotic prescription with no prescription for an antipsychotic in the preceding 180 days</p>	<p>Categorical variable</p> <p>0 = First-generation agent</p> <p>1 = Second-generation agent</p>	<p>Excluded if:</p> <ul style="list-style-type: none"> ➤Received more than one antipsychotic
Specific second-generation antipsychotic agent	Index prescription classified according to the specific second-generation antipsychotic	<p>Categorical variables</p> <p>1 = Clozapine</p> <p>2 = Olanzapine</p> <p>3 = Quetiapine</p> <p>4 = Risperidone</p> <p>5 = Ziprasidone</p>	<p>Excluded if:</p> <ul style="list-style-type: none"> ➤Received more than one antipsychotic

Appendix C: Detailed Description of Study Variables (continued)

Variable	Definitions	Categories	Comments
Medications continued			
Mean daily dose (MDD)	Daily dose inferred from the product of the quantity and strength of the drug dispensed divided by the number of days supplied	Continuous variable	Included only if: ➤ MDD (mg): $12.5 \leq \text{Clozapine} < 1600$ $1.25 \leq \text{Olanzapine} < 80$ $12.5 \leq \text{Quetiapine} < 2400$ $0.125 \leq \text{Risperidone} < 16$ $10 \leq \text{Ziprasidone} < 260$
Duration of antipsychotic therapy	Length of time (days) between the index date and a study endpoint. Endpoint defined as occurrence of any of the following: ➤ Date of development of new-onset diabetes ➤ Date of switching of antipsychotic therapy ➤ Date of addition of a second antipsychotic agent ➤ Date of discontinuation of therapy where discontinuation of therapy defined as no refill of therapy within (days supply x 1.5) of the last refill date	Continuous variable	
Concomitant diabetogenic medications	Treatment with an agent known to increase the risk of diabetes defined as a redeemed prescription for : β -adrenergic blockers; glucocorticoids; oral contraceptive pills containing norgesterol; phenytoin; thiazide diuretics and valproic acid	Categorical variable: 0 = No concomitant diabetogenic therapy 1 = Concomitant diabetogenic therapy	Included only if treatment occurred during the interval between the index date and the study endpoint.

Appendix D: List of Variables from the Texas Medicaid Database

File Name		Data Fields					
Eligibility	ID	Gender	Race	Start	End		
Medications	ID	NDC code	Date	Quantity	Day Supply	Age	Gender
Medical Claims	ID	ICD-9 Diagnoses	Start	End	Primary Diagnosis		
File Name		Description of Variables Contained within Each File					
Patient							
ID	A unique number not based on SSN (necessary for aggregating data files)						
Gender	Patient's gender						
Race	Patient's race						
Min_start	Date patient first enrolled in Medicaid						
Min_end	Date patient discontinued Medicaid enrollment						
Medication							
ID	A unique number not based on SSN (necessary for aggregating data files)						
NDC Code	Drug class code which identifies the drug preparation and strength						
Date	Date drug was dispensed						
Quantity	Quantity of the drug dispensed						
Day Supply	Number of days of the drug supplied (entered by the dispensing pharmacist)						
Age	Patient's age (in years) at date of dispensing						
Gender	Patient's gender						
Medical Claims							
ID	A unique number not based on SSN (necessary for aggregating data files)						
ICD-9	Patient's diagnosis based on ICD-9 code (up to 5 entries per claim)						
From	Date claim started						
To	Date claim ended						
Primary Diagnosis	Primary diagnosis assigned for that claim						

Abbreviations: SSN - Social Security Number; NDC – National Drug Classification
ICD-9-International Classification of Diseases, Ninth Revision.

Appendix E: Summary of Mental Disorder Diagnoses and Related ICD-9 Codes Stratified by Category

Diagnosis	ICD-9 Code
Schizophrenic Disorders	
Simple type	295.0
Disorganized type	295.1
Catatonic type	295.2
Paranoid type	295.3
Acute schizophrenic episode	295.4
Latent schizophrenia	295.5
Residual schizophrenia	295.6
Schizo-affective type	295.7
Other specified types of schizophrenia	295.8
Unspecified schizophrenia	295.9
 Bipolar Affective Disorders	
Manic disorder, single episode	296.0
Manic disorder, recurrent episode	296.1
Major depressive disorder, single episode, severe, specified as with psychotic behavior	296.24
Major depressive disorder, recurrent episode, severe, specified as with psychotic behavior	296.34
Bipolar affective disorder, manic	296.4
Bipolar affective disorder, depressed	296.5
Bipolar affective disorder, mixed	296.6
Bipolar affective disorder, unspecified	296.7
Manic-depressive psychosis, other and unspecified	296.8
 Dementias	
Senile dementia, uncomplicated	290.0
Presenile dementia	290.1
Senile dementia with delusional or depressive features	290.2
Senile dementia with delirium	290.3
Arteriosclerotic dementia	290.4
Other specified senile psychotic conditions	290.8
Unspecified senile psychotic condition	290.9

Appendix E: Summary of Mental Disorder Diagnoses and Related ICD- Codes Stratified by Category (Continued)

Diagnosis	ICD-9 Code
Other Psychotic Disorders	
Alcoholic psychoses	291.x
Drug psychoses	292.x
Transient organic psychotic conditions	293.x
Other organic psychotic conditions	294.x
Other and unspecified affective psychoses	296.9
Paranoid states	297.x
Other nonorganic psychoses	298.x
Psychoses with origin specific to childhood	299.x
Other Non-Psychotic Disorders	
Major depressive disorder, single episode, not specified as with psychotic behavior	296.20 – 296.23
	296.25 – 296.26
Major depressive disorder, recurrent episode, not specified as with psychotic behavior	296.30 – 296.33
	296.35 – 296.36
Neurotic Disorders	300.x
Personality Disorders	301.x
Sexual deviations and disorders	302.x
Alcohol dependence syndrome	303.x
Drug dependence	304.x
Nondependent abuse of drugs	305.x
Psychological malfunction arising from mental factors	306.x
Special symptoms or syndromes, not otherwise classified	307.x
Acute reaction to stress	308.x
Adjustment reaction	309.x
Specific nonpsychotic mental disorders due to organic brain damage	310.x
Depressive disorder, not elsewhere classified	311.x
Disturbance of conduct, not elsewhere classified	312.x
Hyperkinetic syndrome of childhood	314.x
Specific delays in development	315.x
Psychic factors associated with diseases classified elsewhere	316.x

Note: Exclude: ICD-9: 313 (Disturbance of emotions specific to childhood and adolescence) as not relevant to study; and 317-319 (Mental retardation) due to difficulty of diagnosing comorbid mental disorders in patients with mental retardation.

Source: International Classification of Disease - 9th Revision - Clinical Modification (ICD-9-CM)

Appendix F: List of Antihyperlipidemic Agents

Class	Medication
Bile Acid Sequestrants	Cholestyramine Colesevelam Colestipol
Fibric Acid Derivatives	Clofibrate Fenofibrate Gemfibrozil
HMG-CoA Reductase Inhibitors	Atorvastatin Cerivastatin ¹ Fluvastatin Lovastatin Pravastatin Simvastatin Rosuvastatin ²
Other Antilipemic Preparations	Ezetimibe ² Niacin (nicotinic acid)

¹ Withdrawn from the U.S. market 08/08/2001.

² Not available on the U.S. market during the study period (01/01/1997 – 12/31/2001).

Source: Drug Facts and Comparisons³⁹⁰

Appendix G: Variables Included in the Logistic Regression Model Comparing the Prevalence of Diabetes according to Primary Mental Disorder Diagnosis

Model
<i>X₁: Age</i>
<i>X₂: Gender</i>
<i>X₃: Race / Ethnicity</i>
<i>X₄: Primary mental disorder diagnosis</i>
<i>X₅: Hypertension</i>
<i>X₆: Dyslipidemia</i>
<i>X₇: Concomitant diabetogenic mediations</i>

Appendix H: Variables Included in the Logistic Regression Models Comparing the Incidence of Diabetes by Class of Antipsychotic Agent, Specific Second-Generation Antipsychotic Agent, Dose of the Specific Second-Generation Antipsychotic and Primary Mental Disorder Diagnosis for the Specific Second-Generation Antipsychotic Agents

Model 1¹	Model 2²	Model 3³
<i>X₁: Age</i>	<i>X₁: Age</i>	<i>X₁: Age</i>
<i>X₂: Gender</i>	<i>X₂: Gender</i>	<i>X₂: Gender</i>
<i>X₃: Race / Ethnicity</i>	<i>X₃: Race / Ethnicity</i>	<i>X₃: Race / Ethnicity</i>
<i>X₄: Primary mental disorder diagnosis</i>	<i>X₄: Primary mental disorder diagnosis</i>	<i>X₄: Primary mental disorder diagnosis</i>
<i>X₅: Hypertension</i>	<i>X₅: Hypertension</i>	<i>X₅: Hypertension</i>
<i>X₆: Dyslipidemia</i>	<i>X₆: Dyslipidemia</i>	<i>X₆: Dyslipidemia</i>
<i>X₇: Class of antipsychotic</i>	<i>X₇: Specific antipsychotic agent</i>	<i>X₇: Mean daily dose of antipsychotic</i>
<i>X₈: Adherence to antipsychotic therapy</i>	<i>X₈: Mean daily dose of antipsychotic</i>	<i>X₈: Adherence to antipsychotic therapy</i>
<i>X₉: Persistence with antipsychotic therapy</i>	<i>X₉: Adherence to antipsychotic therapy</i>	<i>X₉: Persistence with antipsychotic therapy</i>
<i>X₁₀: Concomitant diabetogenic mediations</i>	<i>X₁₀: Persistence with antipsychotic therapy</i>	<i>X₁₀: Concomitant diabetogenic mediations</i>
	<i>X₁₁: Concomitant diabetogenic mediations</i>	

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1. Model 1 will be used to compare the incidence of diabetes by class of antipsychotic agent (first-generation vs. second-generation).
 2. Model 2 will be used to compare the incidence of diabetes according to the specific second-generation antipsychotic agent (clozapine, olanzapine, quetiapine, risperidone or ziprasidone).
 3. Model 3 will be used to compare the incidence of diabetes according to the dose of antipsychotic used and according to the primary mental health diagnosis for each of the specific second-generation antipsychotic agents: clozapine, olanzapine, quetiapine, risperidone and ziprasidone.

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